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THE PHILADELPHIA PULMONARY NEOPLASM RESEARCH PROJECT: AN INTERIM REPORT * †

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THE Philadelphia Pulmonary Neoplasm Research Project was begun in 1951, primarily to study the natural history of lung cancer with special emphasis on the chronologic relationship between symptoms and roentgenographic changes. Over the next four years, 6,137 men 45 years of age or older were enrolled. To our knowledge, this is the first such study done on a statistically significant group of older men. A preliminary report published in 1955 [1] covered the first 3,945 men who had joined the Project; there were 37 proved primary lung cancers among them. This interim report is concerned with the entire group of 6,137 men and the 92 proved lung cancers found among them during the three and one-half to seven and one-half year follow-up period ending June 3, 1959.

METHOD

From December 4, 1951, to December 4, 1955, every man 45 years of age or older who presented himself for a chest x-ray at the Central Unit of the Philadelphia Tuberculosis and Health Association was invited to join

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the Project and to report twice a year for 70 mm. chest photofluorograms and questioning about any symptoms. The group of 6,137 men (Table 1) is not a random sample of older Philadelphia men. However, symptomatic and radiologic status was known from the start, enabling comparisons to be made between symptomatic and asymptomatic men.

The questionnaire elicits information on respiratory symptoms, smoking habits, presence of diabetes or family history of diabetes, and hospitalizations. Weight is recorded at each visit. From the beginning there were dual readings on abnormal films but, since September, 1956, all films have been read by two physicians independently and by a third physician if there is disagreement between the first two readers or if a significant abnormality occurs.

At the start of the Project, five symptoms were considered to be major for the detection of *early* cancer: (1) cough for months or years; (2) worsening cough; (3) hemoptysis; (4) unilateral wheeze; and (5) weight

TABLE 1

Prevalence of Proved Primary Lung Cancer on Entry by Source of Referral

Basic Group		Source of Referral	Proved Primary Lung Cancer	
No. of Men	Per Cent Distrib.		No.	%
6,137	100.0	Total	66	1.1
1,138	18.5	Survey retake	20	1.8
2,371	38.6	Private physician	36	1.5
1,066	17.4	Self	7	0.7
364	5.9	Clinic	2	0.5
1,198	19.5	Pre-employment	1	0.1

Note: Status as of June 3, 1959.

loss of more than 10 pounds. Because, on entry, one out of every four men had had cough for months or years, chronic cough was dropped as an indication for physician-interview, although still included among the recorded symptoms. If any one of the other four major symptoms or x-ray abnormality develops, the man is requested to return for physician-interview and for 14″ by 17″ films of the chest. Other symptoms, such as chest pain or hoarseness, were not used as indications for physician-interview because it was felt that these symptoms are commonly caused by disease other than lung cancer. When they are manifestations of carcinoma of the lung, they usually occur at an advanced stage when radiologic abnormality is obvious enough to lead to physician-interview. The interviewing physician recommends appropriate clinical action either through the private physician or, if there is none, by referral to a physician, clinic, or hospital. To maintain follow-up on all members, no undue pressure is exerted upon them to accept the recommendations.

Most members are hospitalized at institutions having an active thoracic team. Therefore, unusually complete information is obtainable on most chest cases. Histologic descriptions, autopsy protocols, and representative tissue sections are collected on proved cases of bronchogenic carcinoma. Data are secured on all incidental hospitalizations, regardless of cause, and on diagnostic studies and treatment.

Of the 92 proved lung cancer cases discovered between December 4, 1951, and June 4, 1959, 51 were read as suspect for neoplasm on entry and were promptly diagnosed. Four not suspected of neoplasm on the initial x-ray were promptly hospitalized as having pneumonitis, etc., while one was hospitalized because of hemoptysis. The remaining 36 cases were not suspected of lung cancer until six months or more after entry into the Project.

An experiment was devised to determine by jury review whether the cancer was recognizable on entry films, or prior to the first film routinely read "neoplasm," in the 36 cases mentioned above.

Miniature chest x-rays were assembled haphazardly into rolls. These included films on the 36 cancer cases under study, and films on other members of the Project. Each roll was read independently by five experienced readers. If three of the five readers recognized carcinoma at the site where the cancer later was visualized, neoplasm was considered to have been present roentgenographically on entry into the Project. Prevalence was then calculated on the basis of proved lung cancer visible on the initial films.

By means of this roentgenologic reviewing device, the recognizable onset of cancer could be dated with fair precision. It was found that 26 of the 36 cancer cases were "new," i.e., recognizable only *after* entry into the Project, and that the remaining 10 cases were "old," i.e., present on entry. Among the 26 "new" cases there were three that were recognized earlier by this method than they had been by routine reading. Recognition in these cases was pushed back six months, 23 months, and 25 months respectively.

Since survival rates suggest that the natural history of lung cancer varies markedly with tissue type, and since the pathologic classification of lung cancer is complex and controversial, tissue diagnoses are noted in two ways: (1) the precise diagnosis given by the examining pathologist, and (2) the diagnosis according to a modified WHO classification being used by a group of pathologists in the Veterans Administration.[2] A characteristic tissue section on each tumor has been obtained for jury review in a subsequent study.

Results: Lung Cancer Among P.N.R.P. Men

A. CANCER PREVALENCE ON ENTRY

There were 66 proved lung cancers in men whose initial films revealed abnormalities at the cancer sites. The fact that the men in the Project are not a random sample may account for the high prevalence rate of 11 per

TABLE 2

Prevalence of Proved Primary Lung Cancer on Entry by Age and Race

Age	All Races				White				Nonwhite			
	Total		Proved Ca.		Total		Proved Ca.		Total		Proved Ca.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total	6,137	100.0	66	1.1	5,534	100.0	53	1.0	603	100.0	13	2.2
45–54	2,841	46.3	12	0.4	2,566	46.4	9	0.4	275	45.6	3	1.1
55–64	2,210	36.0	36	1.6	1,988	35.9	30	1.5	222	36.8	6	2.7
65–74	903	14.7	17	1.9	806	14.6	13	1.6	97	16.1	4	4.1
75 & over	183	3.0	1	0.5	174	3.1	1	0.6	9	1.5	—	0.0

Note: Status as of June 3, 1959.

1,000 among them. Boucot and Sokoloff,[3] reporting on 142,156 Philadelphians x-rayed at two official survey units between 1947 and 1952, found the rate for proved lung cancer among men over 45 to be 2.7 per 1,000, or about one-quarter the figure in this Project.

The true prevalence of lung cancer in older Philadelphia men probably lies between this figure of 2.7 and that of 1 per 1,000, the prevalence among 1,198 men in the Pulmonary Neoplasm Research Project who were reporting for pre-employment films (Table 1). Official Philadelphia surveys include some private physician and self referrals, some of whom undoubtedly have symptoms; but it is unlikely that men with major chest symptoms would report for chest x-rays when their employment was at stake.

By Age and Race: Nonwhites had higher cancer rates at all ages than did whites (Table 2). There was an increase with increasing age, except for men 75 and over. The higher rates for nonwhites were not accounted for by source of referral.

TABLE 3

Prevalence of Proved Primary Lung Cancer on Entry by X-ray Appearance

Basic Group		X-ray Classification	Proved Primary Lung Cancer	
No. of Men	Per Cent Distrib.		No.	%
6,137	100.0	Total	66	1.1
158	2.6	Suspect neoplasm	51	32.3
717	11.7	Tuberculosis*	4	0.6
692	11.3	Other pulm. abnormality	7	1.0
121	2.0	Suspicious	—	0.0
4,449	72.5	Negative†	4‡	0.1

* Including 382 minimal inactives.
† Including 192 cardiacs and aortics.
‡ On review these were found to be erroneous negatives.
Note: Status as of June 3, 1959.

TABLE 4

Prevalence of Proved Primary Lung Cancer on Entry by Major Symptoms

Basic Group		Major Symptoms	Proved Primary Lung Cancer	
No. of Men	Per Cent Distrib.		No.	%
6,137	100.0	Total	66	1.1
3,917	63.8	None of five major symptoms	22*	0.6
2,220	36.2	One or more major symptoms†	44	2.0
287	4.7	Hemoptysis	16	5.6
434	7.1	Weight loss over 10 lbs.	14	3.2
171	2.8	Unilateral wheeze	5	2.9
168	2.7	Worsening cough	4	2.4
1,782	29.0	Cough for months/years	37	2.1

* Only 5 had no respiratory symptoms whatsoever.
† The following symptom categories are not mutually exclusive.
Note: Status as of June 3, 1959.

By X-ray Appearance: Most of the 66 cancers found on entry were at once recognized by x-ray as probable neoplasm (Table 3), indicating the advanced nature of the disease in most of the men who had cancer on entry. The fact that, in four instances, only tuberculosis was suspected, emphasizes the masquerading appearance of some lung cancers.

By Major Symptoms: If one or more of the five major symptoms was present, cancer prevalence was three times higher than in their absence (Tables 4, 5). Hemoptysis was the most important symptom;[4] 5.6% of the 287 men reporting it on entry had cancer. Of the 22 men with cancer on entry who had none of the five major symptoms, only five were completely asymptomatic. Four had as their only symptom cough of a few

TABLE 5

Prevalence of Proved Primary Lung Cancer on Entry by Single Major Symptoms

Basic Group		Major Symptoms	Proved Primary Lung Cancer	
No. of Men	Per Cent Distrib.		No.	%
6,137	100.0	Total	66	1.1
3,917	63.8	None of five major symptoms	22*	0.6
403	6.6	More than one major symptom	23	5.7
1,817	29.6	Only one of five major symptoms	21	1.2
104	1.7	*Only* hemoptysis	2	1.9
63	1.0	*Only* unilateral wheeze	1	1.6
1,313	21.4	*Only* cough for months/years	15	1.1
99	1.6	*Only* worsening cough†	1	1.0
238	3.9	*Only* weight loss over 10 lbs.	2	0.8

* Only 5 had no respiratory symptoms whatsoever.
† When cough has been present for longer than one year.
Note: Status as of June 3, 1959.

weeks' duration; the other 13 were obviously advanced cases with symptoms such as pain and hoarseness.

Among the 765 men with any major symptom and an abnormal x-ray, the prevalence of lung cancer reached 5.4% (Table 6). The 923 asymptomatic men with abnormal films had half as much cancer. There were three symptomatic men with cancer who had "negative" films. While, on retrospective review, these films were considered to be "erroneous negatives," the missed lesions were so insignificant that it is likely that, under field conditions, they would be missed again. It must be emphasized that the tables are based on answers to questions put to the members by clerks.

TABLE 6

Prevalence of Proved Primary Lung Cancer on Entry by X-ray Reading and Major Symptoms

Basic Group		X-ray and Symptoms	Proved Primary Lung Cancer	
No. of Men	Per Cent Distrib.		No.	%
6,137	100.0	Total	66	1.1
765	12.5	Significant x-ray reading and one or more of five major symptoms	41	5.4
923	15.0	Significant x-ray reading and none of five major symptoms	21	2.3
1,453	23.7	Negative x-ray reading and one or more of five major symptoms	3*	0.2
2,996	48.8	Negative x-ray reading and none of five major symptoms	1*	0.0

* On review these were found to be erroneous negatives.
Note: Status as of June 3, 1959.

B. CANCER DEVELOPING AFTER ENTRY

During the three and one-half to seven and one-half year period in which the men in this study have been followed, 26 cases of lung cancer have developed in men with no radiologic evidence of the neoplasm when they entered the Project. The incidence approximates one per 1,000 men per year.

Data on all 26 new cancer cases are of considerable interest, but this presentation will be limited to the 15 men who returned frequently enough so that the natural history of their tumors may be described with considerable accuracy. Earlier films were available on them within six to eight months of the first x-ray in which cancer could be visualized. The date of this first radiologic evidence of cancer is the fixed reference point before which symptoms and earlier radiologic descriptions are dated.

The whole panorama of the development of lung cancer can be viewed only by starting with asymptomatic persons in whose chest x-rays no evidence of the cancer can be seen even on retrospective review. Eight of the 15 men who reported regularly were in this category. Six of these eight

men had negative films on entry, one had asbestosis, and one had minimal tuberculosis. In this interim report, only those cases will be presented in detail whose entry films were negative. Because of the concepts held by some that asbestosis and scars are etiologic factors in lung cancer, the other two cases are also of interest.

The following brief case histories on the six asymptomatic men with unequivocally negative entry films are presented according to tissue diagnoses: undifferentiated carcinoma in two cases, adenocarcinoma in one, squamous in one, and mixed in two.

Case 1. J. J. B., a 60-year-old white veteran on 100% disability for traumatic grand mal incurred in the Navy, had been a heavy cigarette smoker for 49 years. He had no x-ray abnormalities or symptoms when he joined the Project on February 14, 1955. One week later he was hospitalized for pneumonia of the anterior segment of the right upper lobe. Bronchoscopy was normal except for some bleeding tendency around the right middle lobe orifice. On the next four visits, the chest films were negative, but on September 15, 1955, the second visit, the man reported heaviness in the chest, chest pain, and wheezing on the right side. Through a clerical error, he was not referred for physician-interview. On March 15, 1956, the third visit, he had lost nine pounds for no apparent reason, the chest pain had persisted, and dyspnea was present. On September 13, 1956, the fourth visit, he had lost an additional seven pounds and dyspnea was his only symptom. At the fifth visit, March 13, 1957, he had no symptoms at all but he had lost an additional three pounds, or a total of 19 pounds over the previous one and one-half years. In mid-June, 1957, three months after the fifth visit, he developed ankle edema, orthopnea, and paroxysmal dyspnea. He was hospitalized July 29, 1957, with a temperature of 101.4° F., marked clubbing, and a chest film which revealed a small left pleural effusion and widening of the mediastinum. Therapy for acute heart failure was unsuccessful and death occurred on August 17, 1957, five months after a negative chest x-ray and 23 months after his first symptoms. Autopsy revealed multiple hard nodules on the anterior left visceral pleura with a small amount of bloody pleural fluid, a 3 by 5 cm. subpleural undifferentiated carcinoma in the anteromedial portion of the left upper lobe, and enlarged nodes containing metastases at the left hilum, to the left of the trachea, and in the deep cervical region. Dissection of the bronchi revealed no tumor on either side.

Comment: One wonders whether the pneumonia of the anterior segment of the right upper lobe was the first clinical manifestation of tumor. It is of interest that seven months after the pneumonia—21 months before manifest illness due to the cancer and the first radiologic evidence of inoperable neoplasm—this patient reported heaviness and pain in the chest as well as right unilateral wheeze.

The careful autopsy dissection of the bronchi makes it certain that bronchoscopy, even if repeated, would have been grossly negative throughout the course. This tumor originated peripherally. An aerosol apparatus to obtain a specimen of secretions from the distal bronchi might conceivably have aided in diagnosis.

Case 2. A. C., a 49-year-old white worker in a wool processing plant, where he was exposed to wool dust and fumes from scouring and bleaching materials, was a

heavy cigarette smoker for 40 years. He had no symptoms or x-ray abnormalities at his first visit on August 15, 1952. Over the next three and one-half years his chest x-rays were negative. On his second visit, February 17, 1953, he had persistent cough. He did not return for 16 months, until June 9, 1954, when, in addition to cough, he had dyspnea and mid-chest pain. Four months later, in October, 1954, he had a cholecystectomy in connection with which he had a negative chest x-ray. There was an interval of 14 months between the third and fourth visits. On August 3, 1955, cough and dyspnea were still present; a nine-pound weight loss was attributed to the major surgery. At the fifth visit, February 10, 1956, the film showed mottling at the right base; cough and dyspnea were still present and another two pounds had been lost for no apparent cause. Two weeks later a 14″ by 17″ film was negative, so the episode was labelled "pneumonitis." On August 17, 1956, at the sixth visit, cough, dyspnea, and pain in the chest were present. Neoplasm or tuberculosis was suspected because of infiltrations in the left infraclavicular region but the patient postponed hospitalization until December, three months after his wife's delivery. Bronchoscopy revealed "bronchitis"; a left upper lobectomy disclosed a small undifferentiated carcinoma in the apico-posterior division. Death occurred on August 25, 1957, nine months postoperatively, one year after the first unimpressive x-ray evidence of cancer, one and one-half years after a negative chest x-ray, and four and one-half years after his first symptom: cough.

Comment: In cases 1 and 2, both with undifferentiated carcinomas, there were long periods in which symptoms were present while chest x-rays continued to be negative. It is of interest that case 2, a heavy cigarette smoker, had bronchitis seen bronchoscopically.

Case 3. W. T. W., a 51-year-old nonwhite warehouse storekeeper, a moderate cigarette smoker for 35 years, had a negative chest film and no symptoms at his first visit, July 2, 1952. He did not return for 22 months until May 13, 1954, when he was still asymptomatic and his film was again negative. At his third visit, November 19, 1954, hilar shadows were prominent, especially on the left. (An area of emphysema in the left upper third was missed.) The only symptom was unproductive cough for one week. Early in 1955 he changed his residence and direct contact was temporarily lost. However, further follow-up disclosed that, in February, 1955, he had been referred by his private physician to an orthopedic clinic because of pain across the shoulders and in the right chest. He was transferred to the medical clinic in March, 1955, with enlarged cervical nodes. X-rays revealed, in addition to the left hilar abnormality, osteolytic lesions in the pelvis and a mass in the mediastinum. Bronchoscopy on March 29, 1955, revealed "thickening of the left upper lobe orifice," but secretions were negative for malignant cells. Biopsy of a cervical node showed adenocarcinoma. Death occurred on May 2, 1955, one year after a negative film and six months after the first radiologic suggestion of cancer and the concurrent onset of unproductive cough. Cough was the only respiratory symptom, pain due to metastases having been the cause for seeking medical help.

Comment: This adenocarcinoma was probably inoperable from the time it gave rise to its first symptom and radiologic abnormality.

Case 4. H. S., a 50-year-old nonwhite male, had worked as a truck driver, laundry worker, and shipper. He had been a moderate cigarette smoker for 32 years and on October 27, 1953, his first visit, he had no symptoms or x-ray abnormalities. He returned regularly every six months, always asymptomatic and with negative

films until his ninth visit, on November 26, 1957, when one reader felt the chest x-ray was negative while the other suspected neoplasm at the right base because of a vague shadow. The man refused hospitalization because he had no symptoms. At the tenth visit, June 17, 1958, despite progression of the right basal lesion, now suspected of neoplasm by both readers, the patient, still without symptoms, refused hospitalization. In August, 1958, he developed his only symptom, right chest pain, and entered a hospital in September. Supraclavicular node biopsy revealed squamous cell carcinoma. Despite radiation and therapy with nitrogen mustard, death occurred on November 18, 1958, three months after the onset of his first symptom, chest pain, one year after the first radiologic abnormality at the cancer site, and one and one-half years after a negative film. Autopsy revealed metastases from the right lower lobe to both lungs, heart, liver, peritoneum, pancreas, right adrenal, kidneys, nodes, and ribs.

Comment: In this case of squamous cell carcinoma, radiologic abnormalities preceded the first symptom, chest pain, by nine months. Obviously this was a rapidly growing and metastasizing tumor, even though it was a squamous type.

Case 5. A. K., a 48-year-old white machinist, had been a moderate cigarette smoker for 25 years. He reported regularly every six months from the time he joined the Project, June 15, 1955. His films were always negative until his ninth visit, May 7, 1959, when the x-ray revealed a small mass above the left hilum and destruction of a portion of the left sixth posterior rib. He reported dyspnea once, at his seventh visit. At his ninth visit, he had had cough, hemoptysis, a sense of heaviness in his chest, and pain in the left thorax for one week. He was hospitalized promptly; metastases to the skull were present. Rib biopsy revealed predominant adenocarcinoma with squamous elements (a mixed tumor). Bronchoscopy was negative. Despite nitrogen mustard therapy, death occurred on June 30, 1959, two months after the simultaneous appearance of his first symptoms and x-ray abnormalities, and seven months after a negative film.

Comment: Bony metastases were present at the time of the first radiologic abnormalities and symptoms.

Case 6. J. G. M., a 60-year-old white office-worker, was a moderate cigarette smoker for 45 years. He had a negative film and no symptoms at his first visit, May 7, 1953. He failed to return for 10 months until March 8, 1954, at which time, although he had had an unproductive cough for six months and had lost five pounds, his film was still negative and remained so throughout his regular visits over the next two years. He still complained of unproductive cough at his third visit, September 22, 1954, but never thereafter. His weight fluctuated. At his seventh visit, September 20, 1956, one reader noted a nodule in the region of the right clavicle and recent fractures of the left 9th, 10th, and 11th ribs. The second reader noted the fractures only, and a third reader described only emphysema. At the eighth visit, March 21, 1957, all readers suspected neoplasm or tuberculosis because of the nodule described above. The patient refused hospitalization because he had no symptoms, and the private physician would not urge admission because the radiologist to whom he had referred the patient for study had reported: "There is nothing suggestive of neoplasm. There is an old productive lesion at the right apex and first interspace periphery with pleural thickening overlying this area." The lesion had progressed by September 23, 1957, the ninth visit, but the patient, still asymptomatic, continued

to refuse hospitalization and, in fact, was so annoyed by our urging that he refused to return to the Project. He was hospitalized on his own, November 24, 1958, because of dyspnea, weakness, and weight loss over the previous "several months." Generalized lymphadenopathy was present, and before studies could be completed, the patient had a generalized convulsion, went downhill, and died December 14, 1958, 27 months after the first x-ray abnormality, 33 months after a negative chest film, and several months after the onset of dyspnea, weight loss, and weakness. Autopsy revealed "undifferentiated adenocarcinoma with areas of keratinization" (a mixed tumor) in the right lung with metastases to the mediastinal and periaortic nodes, pancreas, vertebral bodies, adrenals, spleen, kidneys, and brain.

Comment: The earliest radiologic sign of cancer was misinterpreted by two physicians and missed by two others, raising the question as to the possibility of picking up solitary nodules when they are quite small.

To summarize, symptoms preceded x-ray abnormalities by many months in the two men with undifferentiated carcinoma; were concurrent with the first radiologic abnormality in the case of adenocarcinoma and in one of the two cases with mixed tumors, while in the case of squamous cell cancer and the other mixed-cancer case, x-ray changes preceded symptoms by nine months and two years, respectively. Since there is no fixed pattern, a feasible case-finding program for asymptomatic older men would be semiannual chest x-rays. Those persons with symptoms deserve not only careful radiologic study but meticulous clinical investigation including bronchoscopy and bronchography.

With respect to the two asymptomatic men who had initial radiologic abnormalities not due to cancer, the man with asbestosis developed a sense of heaviness in his chest as his only symptom 15 months after joining the Project. At that time his x-ray revealed a wedge of density above the left hilum as the first change from the typical disseminated lesions of asbestosis seen in his first two films. Prompt exploration followed negative bronchoscopic and cytologic studies, but the undifferentiated carcinoma was inoperable. He died 23 months after his first symptom and the discovery of the abnormality above the left hilum.

The man with minimal inactive tuberculosis had no change in his right apical lesions until his fifth visit, 25 months after joining the Project, when the abnormality appeared more prominent. He continued to be asymptomatic, bronchoscopy was negative, and after all cultures were negative for tubercle bacilli, his chest specialist finally arranged for a right pneumonectomy three months after the first x-ray worsening. A mixed tumor containing squamous and adenomatous elements was found, as well as an adjacent area of healed tuberculosis. This man died 28 months postoperatively and 31 months after the first x-ray abnormality was recognized as neoplasm.

Earliest Radiologic Abnormality in Lung Cancer: Every effort was made to determine, not only from serial chest x-rays, but from pathologic findings,

the site of origin of the 15 new cancers in men on whom negative films were available within six to eight months of the first x-ray abnormality at the cancer site. The small basic numbers make it inadvisable to discuss percentages, but six of the 15 tumors arose centrally while nine arose peripherally. Of the latter, seven originated as solitary peripheral nodules or masses.

Relationship of Symptoms to Earliest Radiologic Abnormality: Only five men, four of whom reported regularly, were asymptomatic up to the time of the first radiologic evidence of cancer. Two of the four in this group were still asymptomatic at the time of their first x-ray abnormalities, while two reported symptoms concurrently with the first roentgenographic lesion. A sense of heaviness was the only symptom in one, whereas cough, hemoptysis, heaviness, and chest pain were all reported at the time of the first film abnormality in the other (case 5), in whom rib metastases

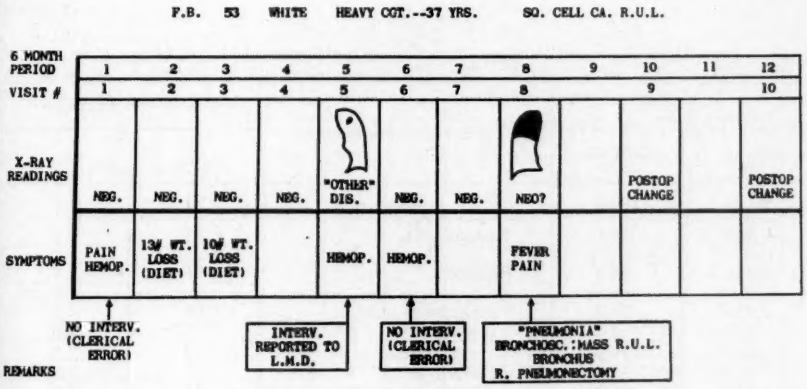
F.B. 53 WHITE HEAVY CGT.--37 YRS. SQ. CELL CA. R.U.L.
6 MONTH PERIOD
VISIT #
X-RAY READINGS
SYMPTOMS
REMARKS
1 2 3 4 5 6 7 8 9 10 11 12
1 2 3 4 5 6 7 8 9 10
NEG. NEG. NEG. NEG. "OTHER" DIS. NEG. NEG. NEO? POSTOP CHANGE POSTOP CHANGE
PAIN HEMOP. 13# WT. LOSS (DIET) 10# WT. LOSS (DIET) HEMOP. HEMOP. FEVER PAIN
NO INTERV. (CLERICAL ERROR)
INTERV. REPORTED TO L.M.D.
NO INTERV. (CLERICAL ERROR)
"PNEUMONIA" BRONCHOSC.: MASS R.U.L. BRONCHUS R. PNEUMONECTOMY

FIG. 1. Chronologic history of case 7.

were present at the time of the first pulmonary change. In the two men whose symptoms developed after x-ray changes, the first symptoms were chest pain seven months after the x-ray abnormality in one instance and weight loss beginning 18 months after the first film lesion in the other.

Survival of Men with New Cancers: Only two of the 26 men with new cancers are alive at this writing. Both had squamous cell carcinoma resected 2½ years ago. One was an irregular visitor; the other was resectable despite several unnecessary delays. The latter case is reported below.

Case 7. F. B., a 53-year-old white machine operator in a steel plant, was a heavy cigarette smoker for 37 years. The chronology of his history is shown in Figure 1. At his first visit, April 3, 1954, his chest x-ray was negative but he reported hemoptysis and "soreness" in his chest. Through a clerk's error he had no physician-interview. At the second visit, September 30, 1954, no further hemoptysis

had occurred but he had lost 13 pounds by dieting. His film was again negative as it was at the third visit, February 24, 1955, when, once more, the only symptom was weight loss of 10 pounds by dieting. No symptoms or x-ray abnormalities were found at the fourth visit, November 19, 1955. On June 9, 1956, the fifth visit, hemoptysis was reported again and there were infiltrations in the upper left lung which had cleared promptly on re-x-ray, so the episode was diagnosed as "pneumonia." On November 26, 1956, the sixth visit, hemoptysis was present but the x-ray was negative. The man was asymptomatic and had a negative film at his seventh visit, May 25, 1957. When due for his eighth visit, he had fever and chest pain for which he was treated unsuccessfully for "pneumonia of the right upper lobe" by his private physician. Hospital admission films of November 23, 1957, revealed atelectasis of the right upper lobe. After a bronchoscopic biopsy revealed squamous cell carcinoma, right pneumonectomy was performed December 19, 1957. There was no evidence of metastasis and this man is alive two and one-half years postoperatively and three years after his last negative film. It is dubious as to whether his hemoptysis and chest soreness when he joined the Project in 1954, 43 months before his first x-ray sign of malignancy, were due to cancer. Yet, to date, he has had no hemoptysis since his resection.

TABLE 7

Prevalence of Proved Primary Lung Cancer by Type and Degree of Smoking

Basic Group		Type and Degree* of Smoking	Proved Primary Lung Cancer	
No. of Men	Per Cent Distrib.		No.	%
6,137	100.0	Total	92	1.5
806	13.1	Nonsmokers	1	0.1
5,331	86.9	Smokers	91	1.7
3,310	53.9	Cigarettes only	68	2.1
523	8.5	Occasional	5	1.0
1,809	29.5	Moderate	39	2.2
978	15.9	Heavy	24	2.5
932	15.2	Cigarettes & pipe/cig.	15	1.6
		Occasional		
372	6.1	Moderate	5	1.3
560	9.1	Heavy	10	1.8
272	4.4	Pipe only	2	0.7
50	0.8	Occasional		
151	2.5	Moderate		
71	1.2	Heavy	2	2.8
560	9.1	Cigars only	3	0.5
113	1.8	Occasional		
253	4.1	Moderate	1	0.4
194	3.2	Heavy	2	1.0
243	4.0	Pipe & cigars	3	1.2
		Occasional		
113	1.8	Moderate	1	0.9
130	2.1	Heavy	2	1.5
14	0.2	Incomplete		

* Heavy smoking is more than one pack of cigarettes, more than four cigars, or more than 10 pipefuls of tobacco per day; moderate smoking is ½–1 pack of cigarettes, 1–4 cigars or 1–10 pipefuls of tobacco per day; occasional smoking is any amount less than moderate.

Note: Status as of June 3, 1959.

C. CANCER AND SMOKING

Since the duration of follow-up on the Project members is relatively short in relation to the mean duration of smoking on entry, the following data are based on the total of 92 cancer cases.

Only one cancer, an undifferentiated carcinoma with some unusual sarcomatous characteristics, was found among the 806 nonsmokers (Table 7), and the increase of cancer with increased degrees of smoking was obvious even in categories other than cigarette smokers. Degrees of smoking are defined in the footnote to Table 7.

There was no relationship to smoking in those who had smoked less than 20 years; only one cancer, an undifferentiated tumor, occurred in a man who was an occasional cigarette smoker (Table 8).

However, with a smoking history of more than 20 years, there was a definite correlation between cancer rate and degree and duration of smoking. This correlation was not appreciably altered when age was taken into account.

TABLE 8

Prevalence of Proved Primary Lung Cancer by Type, Degree, and Duration of Smoking

Type and Degree of Smoking	Smoked Less Than 20 Years			Smoked 20–39 Years			Smoked 40 Years or Over		
	No. of Men	Lung Cancer		No. of Men	Lung Cancer		No. of Men	Lung Cancer	
		No.	%		No.	%		No.	%
Total	1,256	2	0.2	2,814	26	0.9	2,053	64	3.1
Nonsmokers	806	1	0.1						
Smokers	450	1	0.2	2,814	26	0.9	2,053	64	3.1
Cigarettes only	248	1	0.4	1,854	21	1.1	1,208	46	3.8
Occasional	118	1	0.8	241	1	0.4	164	3	1.8
Moderate	91			1,019	11	1.1	699	28	4.0
Heavy	39			594	9	1.5	345	15	4.3
Cigarettes & pipe/cig.	71			463	4	0.9	398	11	2.8
Occasional									
Moderate	33			176	1	0.6	163	4	2.5
Heavy	38			287	3	1.0	235	7	3.0
Pipe only	31			126			115	2	1.7
Occasional	14			25			11		
Moderate	16			65			70		
Heavy	1			36			34	2	5.9
Cigars only	81			269	1	0.4	210	2	1.0
Occasional	26			52			35		
Moderate	42			123			88	1	1.1
Heavy	13			94	1	1.1	87	1	1.1
Pipe & cigars	19			102			122	3	2.5
Occasional									
Moderate	11			45			57	1	1.8
Heavy	8			57			65	2	3.1

Note: Fourteen men with incomplete smoking histories are omitted. Status as of June 3, 1959.

Men who had smoked longer than 40 years had an over-all cancer prevalence of 3.1%. Cigar and pipe smokers began to have high rates, suggesting that the cumulative volume of smoke reaching the alveoli rather than the type of smoke may be the major etiologic factor.[5]

One out of every 23 men in this study who were heavy cigarette smokers for more than 40 years had proved lung cancer.

D. CANCER COMPARED TO ACTIVE TUBERCULOSIS DEVELOPING AFTER ENTRY

Over the same period as that in which the 26 cases of lung cancer developed, 22 cases of proved active tuberculosis were found. However, seven of the tuberculosis cases were reactivations of inactive disease, a phenomenon which does not occur in patients with lung cancer. Comparing the 26 new lung cancer cases with the 15 new cases of active tuberculosis, the incidence of lung cancer was almost twice that of new active tuberculosis.

Discussion

The two major interests of the Philadelphia Pulmonary Neoplasm Research Project are (1) the study of lung cancer prevalence and incidence in populations of older men according to a number of variables such as chronic cough, worsening cough, certain smoking habits, etc. (this approach differs from the usual one which begins with a population of lung cancer cases); and (2) a study of the natural history of lung cancer as it develops in men whose single chest x-rays appear negative. To our knowledge, this is the first study in which a significantly large group of older men—over 6,000—has been conscientiously followed for years in order to determine the chronologic relationship of symptoms to x-ray changes as lung cancer develops.

At this point in the follow-up—three and one-half to seven and one-half years after entry—we believe we have picked up all the cancers which might be seen on the entry films. These numbered 66, among which were four with initial x-ray abnormalities so unimpressive that they were missed at first.

There have been 26 cancers which appeared radiologically during the study period. The addition of a few more cases of bronchogenic carcinoma with serial films is worthwhile *only* if they represent the yield over time of some reasonable population. Then, and only then, does the history of symptoms and x-ray abnormalities reflect primarily the natural history of the disease, rather than the vagaries of selection.

One of the most important findings thus far has been the fact that, of the 15 new lung cancer cases who reported regularly or in whom the natural history of the disease can be adequately delineated, only three had x-ray changes before symptoms. Two had concurrent symptoms and x-ray abnormalities but, in 10 instances, symptoms antedated x-ray changes by as long as five and one-half years, with a mean of two and one-half years.

These findings are in contrast to those of retrospective studies which concentrate their attention on fortuitous serial roentgenograms for the study of the natural history of bronchogenic carcinoma.[6, 7] There is, of course, the problem of uncertainty that the symptoms were due to the cancers. However, if, as the new cancers develop, these preliminary findings hold—i.e., that more than half have respiratory symptoms for long periods of time before radiologic changes appear—it will be of extreme importance to emphasize, even more than we have, the need for extensive radiologic and cytologic studies, as well as bronchoscopy, bronchography, and meticulous clinical investigation.

Summary

The Philadelphia Pulmonary Neoplasm Research Project is a prospective investigation of older men by means of semiannual photofluorograms and questioning about symptoms in order to study the natural history of bronchogenic carcinoma. In 6,137 men over 45 years of age, during a follow-up period of from three and one-half to seven and one-half years, 92 cases of proved bronchogenic carcinoma have been found. Of these, 66 were visible on entry films, a prevalence of 11 per 1,000 in this particular group. Hemoptysis was the most important symptom of lung cancer among these cases.

Twenty-six cases of lung cancer developed during the period of observation, an incidence rate of 1 per 1,000 per year.

Several cases are presented to demonstrate the type of information which is obtainable by this method. Although the number of cases is as yet small, the majority of carcinomas arose in the periphery; symptoms attributable to the neoplasms often appeared before radiologic abnormalities.

The incidence of new, proved lung cancer was twice as high as the incidence of new, proved active tuberculosis.

The correlation between smoking and proved bronchogenic carcinoma in this group of men is of a high order. Lung cancer is related to degree and duration of smoking.

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Summario in Interlingua

Le Projecto Philadelphia de Recercas in Re Neoplasma Pulmonar es un studio prospective de masculos de etates avantiate, a base de un programma de photofluorogrammas e questionarios semiannual visante a clarificar le historia natural de carcinoma bronchogene. In un population de 6.137 masculos de etates de plus que 45 annos, examines periodic durante inter tres annos e medie e septe annos e medie resultava in le discoperta de 92 casos de provate carcinoma bronchogene. In 66 de

istos le condition esseva recognoscibile in le pelliculas initial, lo que corresponde a un incidentia de 11 pro mille in iste population particular. Hemoptysis esseva le plus importante symptoma de cancere pulmonar.

Vinti-sex casos de cancere pulmonar se disveloppava durante le periodo de observation, amontante a un incidentia de un pro mille per anno.

Plure casos es presentate pro demonstrar le typo de information obtenibile per iste methodo. Ben que le numero de casos es ancora micre, certe constatationes pare significative. Le majoritate del carcinomas habeva lor origine in le peripheria. Symptomas attribuibile al presentia de neoplasma se manifestava frequentemente ante le apparition de anormalitates radiologic.

Le incidentia de nove casos de provate cancere pulmonar esseva duo vices le incidentia de nove casos de provate tuberculosis active.

Le correlation inter le habitude del fumar e le presentia de demonstrate carcinoma bronchogene esseva in iste gruppo de masculos de un alte ordine. Cancere pulmonar esseva relationate con le grado e le duration del fumar.

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UNRECOGNIZED AIRWAY OBSTRUCTION ASSOCIATED WITH SMOKING: A PROBABLE FORERUNNER OF OBSTRUCTIVE PULMONARY EMPHYSEMA * †

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INTRODUCTION

AN association between cigarette smoking and chronic obstructive pulmonary disease in patients has been shown by several writers.[1-4] Furthermore, it has been postulated that in such patients, smoking is the cause of the obstructive process. This may be due to inflammatory changes in the lining of the airway that lead to narrowing of the lumen or to distortion of the airway so that the flow of air is impeded.

If smoking is a cause of obstructive pulmonary disease, one would expect to find it in some degree among many who smoke but who do not have manifest disease, provided a sufficiently sensitive index of obstruction is available for screening of large numbers of individuals. A kymographic tracing (Figure 1) obtained during a maximal forced expiratory effort (the expirogram) appears to meet this need.[5] The slope of the tracing at each instant during expiration is a measure of the expiratory flow rate, which becomes progressively slower as expiration proceeds. In practice it is convenient to consider the average rate of expiration between two arbitrarily selected points on the curve. To date considerable experience has been obtained with measurements of the average rate between the point of beginning expiration and the point reached after the elapse of one second (FSV). A more reliable measurement (and the one used herein) can be made by correcting for the patient's failure to exert maximal effort at the start. A third parameter, which is probably more useful,[6] is the average rate of expiration between the points where 25% and 75% of the vital capacity has been expired (E_{25-75}). The usefulness of this parameter as a measure of the degree of obstructive disease has been confirmed elsewhere,[7] and it was further shown that an even more sensitive index may be obtained

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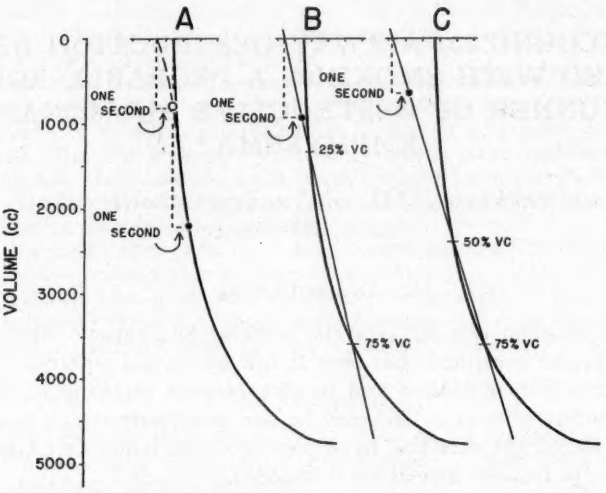

FIG. 1. The interval between the points on the base line was one centimeter, equivalent in time to one second. Expiration was downward and the paper moved from right to left. A. Expiratory tracing (solid line) obtained from a subject with moderate obstructive pulmonary disease. The vital capacity (VC) is read from the scale at the left and in this instance is 4,725 c.c. The first second volume (FSV) is obtained by dropping a perpendicular from the base line at the start of expiration and finding the point at which the tracing has deviated from the perpendicular by a distance of 1 cm. (one second). The FSV is read from the volume scale at the left and in this instance is 2,200 c.c. (solid dot). If the subject had failed to make an adequate effort at the start, the initial portion of the tracing might have had the configuration shown by the dashed line. This would have given an FSV of only 800 c.c. (open dot). However, extension of the steepest portion of the tracing to the base line and measurement from the point of intersection (not shown) will give a value for the FSV which will closely approximate that obtainable with an adequate effort. B. To obtain E_{25-75}, draw a line through the points at which 25% and 75% of the VC has been expired and extend it to intersect the base line. Drop a perpendicular from the point of intersection and find the point (solid dot) at which the line drawn through the two points on the tracing has deviated from the perpendicular by 1 cm. (one second). The E_{25-75}, expressed in c.c./second, is obtained from the scale at the left and in this instance is 950 c.c./sec. C. E_{50-75} can be derived in a similar manner after drawing a line through the points where 50% and 75% of the VC have been expired, giving in this instance 700 c.c./sec.

by measuring the rate of flow during the third quarter of expiration (E_{50-75}), a finding which is in accord with experimental studies and theoretical considerations.[8] Since the vital capacity (VC) is usually decreased in the presence of overt obstructive disease, we have also included this measurement. In this report we present a correlation between the VC, corrected FSV, E_{25-75}, and E_{50-75}, and the smoking habits of employees in an industrial plant.

A number of reports concerned with the acute effects of smoking on pulmonary function have appeared.[9-13] The pertinence of such studies to the subject under consideration is questionable. If smoking is followed by a prompt but temporary change in function, it does not necessarily follow that prolonged smoking can produce persisting changes, and conversely, per-

sisting changes could be induced by smoking over many years in the absence of any measurable change in pulmonary function immediately following the smoking of a cigarette.

Materials and Methods

Tracings of forced expiration following a maximal inspiration were obtained using a six-litre recording spirometer with a kymograph speed of 1 cm. per second (Collins Vitalometer *). Usually, two tracings were made, but in some instances more attempts were required before reproducible curves were obtained. All tests were done at a single sitting and measured later without reference to the clinical record or smoking history.

Measurements were made of the vital capacity (VC), the "corrected" first second volume (FSV), the rate of expiration between the points where 25% and 75% of the VC (E_{25-75}) and the points where 50% and 75% of the VC (E_{50-75}) had been expired. The "corrected" FSV was obtained by first extending the steepest segment of the curve to the base line and then making the measurement from the point where the extended line met the base line (Figure 1). The slope of a line drawn through the points where 25% and 75% of the vital capacity had been expired gave the E_{25-75} [6] and that where 50% and 75% of the vital capacity had been expired gave the E_{50-75}.[14] Of the two or more tracings obtained, the one giving the highest value for each of these parameters was selected irrespective of the value it gave for the others. Thus the value for the FSV might be obtained from one tracing and that for the VC from another. Ten subjects were eliminated because of unsatisfactory expirograms.

The subjects for this study were selected from approximately 1,000 apparently healthy factory workers on the bases of age and sex only. As part of a study of respiratory allergic disease, expirograms were obtained, and questionnaires dealing in detail with respiratory symptoms were filled out in conjunction with a routine annual or pre-employment medical examination, which included x-ray examination of the chest.† We made no attempt to prevent smoking prior to the examination although smoking was not permitted in the examining rooms or laboratories of the medical department. Patients first disrobed and went to the laboratory for blood and urine examinations, which were followed by tests of pulmonary function. Those persons with cardiac disease or pulmonary disease were eliminated from consideration without reference to the smoking history or tests of pulmonary function. Of the 23 thus eliminated nine had probable bronchial asthma; there were five in whom a diagnosis of cardiac disease had been made; there were five with pulmonary fibrosis by x-ray, with or without bronchiectasis; and there were single cases of kyphoscoliosis, cystic disease

* Warren E. Collins Inc., 555 Huntington Avenue, Boston 15, Massachusetts. The apparatus contained neither valves nor a CO_2 scrubber.

† We wish to thank the medical department of the Gillette Safety Razor Company for their help in carrying out this study.

of the lungs, elevated hemidiaphragm by x-ray, and thoracotomy for empyema.

Since an effect of smoking on pulmonary function, if such an effect exists, would presumably be more easily detected among those who had smoked for many years, we elected to consider only those over the age of 40. Because there were too few females for a statistically adequate sample, we considered males only. Those over the age of 60 were eliminated in order to obtain a more uniformly distributed sample. This is an important consideration, since a history of smoking for 15 or more years would be required in most instances to establish an exposure to tobacco smoke which would lead us to place an individual in the group of "heavy smokers" (see below), and therefore, this group would tend to become more heavily weighted with older individuals. This point will be discussed below.

The amount of smoking by individuals was expressed in "pack years," the product of the average number of packs of cigarettes smoked per day and the number of years of smoking. Cigar- and pipe-smoking was converted into the same units by assuming one pipeful as being equivalent to three cigarettes and one cigar equivalent to five cigarettes. These assumptions are admittedly questionable, and the influence of this conversion on the results will be discussed. Since the number of individuals who had never smoked was very small, the measurements of expiratory flow rate in a group of "light smokers," consisting of the nonsmokers and those who had smoked less than 10 "pack years," were compared with measurements obtained in a group of "heavy smokers," consisting of those who had smoked 30 "pack years" or more. Fifty "intermediate smokers" who smoked 10 to 29 "pack years" were excluded from the comparison.

Results

Mean values for the VC, the FSV, the E_{25-75} and the E_{50-75} are given in Table 1 for the entire group of male subjects between ages 40 and 60, and for the "light smokers" and the "heavy smokers" separately. In the fourth column are shown the t values for the difference between group mean, and in the fifth column the value for p, which indicates the probability that

Table 1

Mean Values for Parameters of Pulmonary Function. Male Employees, Aged 40–60

	Total	"Light Smokers"	"Heavy Smokers"	t	p
Number	(213)*	(59)	(104)		
VC (c.c.)	3,646± 608†	3,703± 558	3,578± 642	1.39	0.16
FSV (c.c.)	2,565± 657	2,670± 685	2,489± 644	1.49	0.14
E_{25-75} (c.c./sec.)	2,780±1,118	3,011±1,095	2,656±1,126	2.02	0.04
E_{50-75} (c.c./sec.)	2,417±1,045	2,710±1,075	2,284± 985	2.57	<0.01

* This column includes 50 "intermediate smokers" (10–29 pack years).
† Standard deviation

the differences observed could occur by chance alone. The E_{25-75} difference is slightly greater than that required to give significance at the 5% level; the E_{50-75} difference is significant at the 1% level. The VC and FSV differences are not statistically significant, although it will be noted that the differences are in the same direction as those for E_{25-75} and E_{50-75}.

Discussion

The results of these studies indicate that among heavy smokers the mean expiratory flow rate during the third quarter of maximal forced expiration (E_{50-75}) was approximately 20% below that of light smokers. The observed reduction in flow rate, presumably due to airway obstruction, was not sufficient to cause symptoms in most instances. Even those individuals who had relatively more obstruction did not indicate on the questionnaire that they were aware of difficulty, feeling perhaps that their exercise tolerance was normal for their age. Patients seen on the wards, in outpatient clinics, and in private practice with symptomatic asthma and emphysema, on the other hand, usually have values for E_{25-75} or E_{50-75} which are less than 50% of normal.[7]

Both E_{50-75} and E_{25-75} decrease with age, and as pointed out in the section on Methods, one would expect a preponderence of older individuals among the "heavy smokers." However, the mean age of the "heavy smokers" was only slightly greater than that of the "light smokers" (49.5 years vs. 47.9 years). Based on this age difference, we can account for less than 10% of the difference noted between the E_{50-75} values of the two groups. Age differences between the "heavy smokers" and "light smokers," therefore, do not appreciably alter the significance of the results.

The apparent effect of smoking on expiratory flow rate may have been somewhat greater than is evident from the data presented since "heavy smokers" were compared with "light smokers" and not with nonsmokers. In the group classified as "light smokers," it is possible that a small reduction in pulmonary function also existed. Furthermore, the group of "heavy smokers" included those who had smoked primarily cigars and pipes. There were 16 such individuals with a mean E_{50-75} of 2,670 c.c./sec. Since this is close to the mean value for "light smokers," pipe and cigar smoking may not be so deleterious as cigarette smoking. This may be due to the lesser tendency for cigar and pipe smokers to inhale or to our inability to estimate the equivalence of pipes or cigars in terms of cigarettes. Regardless of the reason for the difference, the exclusion of cigar and pipe smokers from the group of "heavy smokers" would have increased the difference between this group and the "light smokers" by almost 10%.

Since our sample was drawn from those gainfully employed, one would not expect to find the extreme pulmonary abnormality characteristic of obstructive disease. Therefore, the ability to demonstrate a significant reduction in the mean value of a measure of airway obstruction indicates

that a degree of obstruction must be widespread among the members of the group and not peculiar to a few.

There have been conflicting reports concerning the effect of smoking on pulmonary function in normal individuals. A correlation between tobacco smoking and residual pulmonary volume which was significant at the 5% level was shown in 58 healthy male subjects.[9] In this group there was also a negative correlation between smoking and vital capacity, but not enough to fulfill the usual criteria for statistical significance. Attinger and Segal,[10] in a study of 20 subjects, concluded that "statistically, there is no difference in the mechanics of breathing in the control state between smokers and nonsmokers." The observed reduction in compliance [12] and increase in airway resistance [11, 13] in patients with emphysema immediately following the inhalation of cigarette smoke may be irrelevant, since the patients with disordered function may respond to a stimulus in an abnormal manner even though that stimulus is not causally related to the disorder. For example, asthmatic patients who have never smoked may have their asthma precipitated by the inhalation of tobacco smoke. On the other hand, if there were an acute effect of smoking on air flow in normal individuals this could influence our results, because "heavy smokers" would be likely to smoke just prior to their medical examination. However, studies of the acute effect of smoking [10, 12] in normals do not indicate that changes of the order of magnitude noted would be produced thereby.

Since this study was completed a study has appeared [15] in which the maximal expiratory flow rate determined by "puff meter" is used as a measure of bronchial obstruction. Although this study dealt with patients in the hospital rather than normal subjects, the results are strikingly similar to those presented herein.

We believe that the observed reduction in expiratory flow rate among smokers is the forerunner of chronic obstructive emphysema. Presumably factors other than the mere number of cigarettes smoked play a role in determining the rate at which obstruction develops, as well as the degree attained. Individual susceptibility, intercurrent infections, and the manner in which cigarettes are smoked may all be factors. It has been postulated [16] that the personality of the individual who smokes heavily differs from the one who does not, and that this rather than smoking per se accounts for the greater mortality from cancer and other disease in such individuals. It seems to us most unlikely that such individuals would also have poorer lung function. On the other hand, if smoking does cause bronchial obstruction, this may decrease the chances of survival in many apparently unrelated situations such as myocardial infarction, cardiac failure, or surgery for cancer of organs other than the lung. This may explain in part the greater overall mortality observed among smokers in recent prospective studies [17, 18] which would indicate that the absolute number of deaths directly and indirectly attributable to smoking would far exceed those arising from lung

cancer alone. However, the relationship would be more difficult to establish than that for lung cancer alone, since deaths from such common causes would be relatively frequent among both smokers and nonsmokers.

Summary and Conclusions

Among 213 male factory workers between the ages of 40 and 60, "heavy smokers" had a mean value for the rate of expiration during the third quarter of forced expiration which was approximately 20% less than that of "light smokers." This difference was significant at the 1% level. This reduction in flow rate was not associated with dyspnea in most instances. We believe this change to be similar to that present to a more marked degree in patients with chronic obstructive emphysema, and feel that it supports a causal relationship between smoking and chronic obstructive pulmonary emphysema.

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Summario in Interlingua

Esseva obtenite registrationes de expiration fortiate post inspiration maximal, con le uso de un spirometro registratori de 6 litros, a un velocitate del kymographo de 1 cm per secunda (Vitalometro de Collins). Usualmente duo registrationes esseva effectuate, sed in un numero de casos plure essayos esseva requirite ante que reproducibile curvas esseva obtenite. Omne le tests esseva completate in un sol session. Le mesurationes esseva executate subsequentemente sin referentia al documentation clinic o al historia del fumar.

Esseva mesurate: Le capacitate vital (CV); le volumine del prime secunda (VPS); le intensitate del expiration inter le punctos ubi 25% e 75% del CV esseva expirate (E_{25-75}); e le intensitate del expiration inter le punctos ubi 50% e 75% del CV esseva expirate (E_{50-75}). Le inclination del linea traciate inter le punctos in que 25% e 75% del CV esseva expirate representava le E_{25-75}, e le inclination del linea traciate inter le punctos in que 50% e 75% del CV esseva expirate representava le E_{50-75}.

Inter 213 travaliatores mascule de fabrica de etates de inter 40 e 60 annos, "forte fumatores" habeva un valor medie pro le intensitate del expiration durante le tertie quartiero del expiration fortiate le qual esseva approximativemente 20% infra illo de "leve fumatores." Iste differentia esseva significative a un nivello de 1%. In le majoritate del casos, le relentation del fluxo non esseva associate con dyspnea. Nos opina que il se tracta hic de un alteration simile a illo incontrate—a grados plus marcate—in patientes con chronic emphysema obstructive e que iste constatation supporta le these de un relation causal inter le habitude del fumar e le occurrentia de chronic obstructive emphysema pulmonar.

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ELECTROCARDIOGRAPHIC AND VECTORCARDIOGRAPHIC DETECTION OF HEART DISEASE IN THE PRESENCE OF THE PRE-EXCITATION SYNDROME (WOLFF-PARKINSON-WHITE SYNDROME) * †

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It is well known that the electrocardiographic diagnosis of myocardial disease, particularly of myocardial infarction, in the presence of left bundle branch block (LBBB) is difficult. However, it has been shown recently that the spatial vectorcardiogram (sVCG) can be useful in the diagnosis of myocardial disease in the presence of LBBB.[1, 2] Many investigators have considered the electrocardiographic diagnosis of myocardial disease difficult in the presence of the pre-excitation syndrome (Wolff-Parkinson-White syndrome) for essentially the same reasons as in LBBB.[3, 4, 5] Because of the diagnostic possibilities of the sVCG in LBBB, it was decided to investigate the value of the spatial vectorcardiogram in diagnosis in the presence of the pre-excitation syndrome. This report also includes a general description of the spatial vectorcardiogram and the ventricular gradient in the Wolff-Parkinson-White syndrome.

Materials and Methods

Spatial vectorcardiograms were recorded in 15 patients with the pre-excitation syndrome employing the equilateral tetrahedral reference system previously described.[6] The ages of the patients ranged from 14 to 59 years, the mean being 32 years (Table 1). Eleven of the patients were male and four were female; nine were white and six Negro. Eight of the 15 patients had evidence of heart disease (Table 1). One of the eight patients with heart disease was studied at necropsy.

The ventricular gradient ($\hat{G}$) was calculated as previously described.[7] The normal values used in this study for $\hat{A}_{QRS}$ were $-21.5°$ to $104.9°$ and 3.1 to 40.6 μv.s., and for $\hat{G}$, $2.2°$ to $72.2°$ and 13.5 to 78.9 μv.s. These

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TABLE 1

The Clinical Data on the 15 Patients with Wolff-Parkinson-White Syndrome

Patient No.	Age	Sex	Race	Clinical Diagnosis
1	32	M	W	Normal
2	21	M	C	Normal
3	22	M	W	Normal
4	44	M	C	Normal
5	15	F	W	Normal
6	23	M	W	Normal
7	38	M	W	Normal
8	42	M	W	Arteriosclerotic heart disease
9	28	F	W	Rheumatic heart disease
10	39	M	W	Hypertensive cardiovascular disease
11	20	F	C	Hypertensive cardiovascular disease
12	59	M	C	Arteriosclerotic heart disease
13	40	M	W	Arteriosclerotic heart disease
14	49	M	C	Arteriosclerotic heart disease
15	14	F	C	Rheumatic heart disease

values were calculated from Ashman's data for adult men and women; the ranges are equal to twice the average standard deviations.[8]

RESULTS

The Electrocardiogram: The electrocardiographic patterns of Wolff-Parkinson-White syndrome observed in the 15 patients of this series were of the four types previously described[9] (Figure 1). Ten patients had Type A configuration, three Type B, one Type C, and one Type D. The P-R interval averaged 0.10 sec. (range, 0.08 to 0.12 sec.). The average QRS duration was 0.14 sec. (range, 0.11 to 0.18 sec.). Figure 1 is a schematic representation of the possible alterations in the order of depolarization which produced the four common electrocardiographic patterns encountered in the Wolff-Parkinson-White syndrome. Because the electrocardiographic characteristics of this syndrome have been discussed extensively in reports from this[9,10] as well as other laboratories,[11-15] the electrocardiographic patterns are only briefly reviewed.

Type A (10 Patients): The configuration of the QRS complex in the uncomplicated Wolff-Parkinson-White syndrome is determined by the anatomic site of the anomalous pathway or the site of initiation of ventricular depolarization, and the length of time the normal impulse is delayed in the A-V node. In the majority of patients the aberrant pathway terminates, or ventricular depolarization is initiated, at the base of the right ventricle. It has been shown by means of simultaneous intracardiac, esophageal, and extremity leads that in the Wolff-Parkinson-White syndrome the ventricular myocardium is activated from epicardial to endocardial levels.[16] When the process of ventricular activation is initiated at the base of the right ventricle,

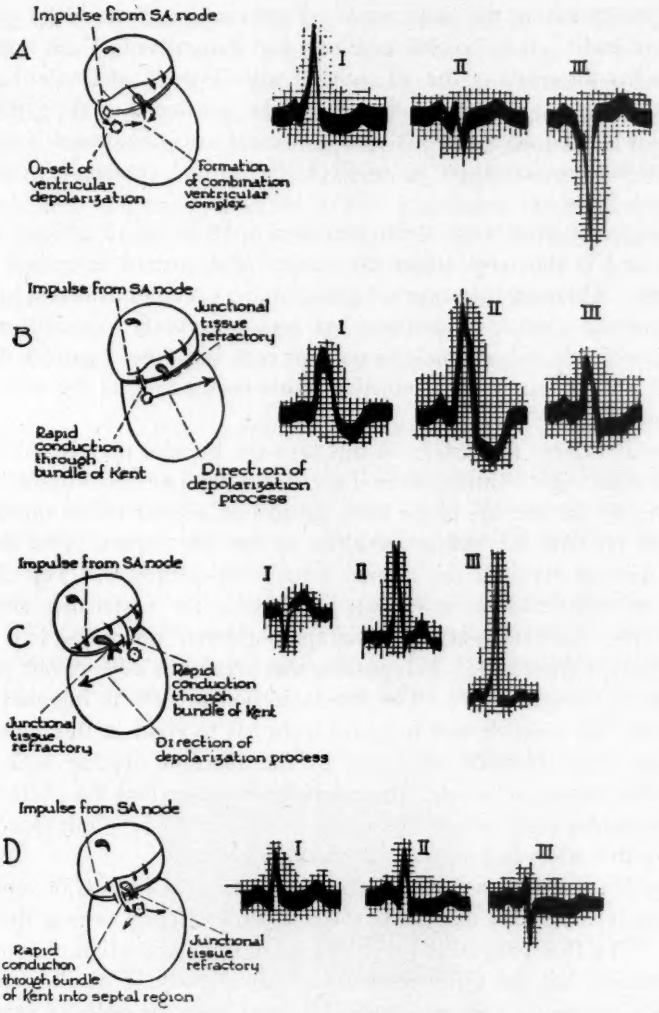

FIG. 1. Electrogenesis of four types of electrocardiograms in the Wolff-Parkinson-White syndrome. Type A is the most frequently encountered type. See text for details. (From Burch and Winsor: A Primer of Electrocardiography; reprinted with the permission of Lea & Febiger.)

the migration of electric forces can be indicated in general by a vector directed from right to left. The aberrant order of depolarization results in a positive and usually slurred or deformed initial deflection in leads I and II and a negative initial deflection in lead III. This deformed initial de-

flection is known as the delta wave. Furthermore, if the delta wave is positive in lead V_2, it is directed anteriorly and if negative in V_2, it is directed posteriorly. In seven of the 10 patients with Type A electrocardiograms the delta wave was positive in lead V_2. The remainder of the QRS complex following the delta wave is usually normal in configuration and represents ventricular activation by way of the normal conducting pathways (Figure 1, Type A).

This type of electrocardiogram was seen in 10 of the 15 patients studied (66%) and is the most frequently encountered pattern described in the literature. Although there are not many autopsy studies available in which the anomalous conduction pathway has been adequately localized, most of the studies that have been made on patients with this type of pattern describe aberrant cardiac muscle or conduction tissue terminating at the base of the right ventricle.[17-19]

Type B (Three Patients): In this type the impulse may be initiated at the base of the right ventricle as in Type A, but the junctional tissue is made refractory by the passage of the early process of depolarization through the bundle of His and the bundle branches, so that the impulse from the atria cannot descend through the normal conducting pathways. The aberrant process of depolarization is entirely responsible for ventricular activation so that the resultant electrocardiographic pattern resembles left bundle branch block (Figure 1). This pattern was present in 20% of our patients.

Type C (One Patient): The depolarization process is initiated at the base of the left ventricle and migrates from left to right in this type. The junctional tissue is made refractory by the aberrant impulse as it passes through the bundle of His and the bundle branches so that the electrocardiogram resembles right bundle branch block (Figure 1). Only one patient (7%) in this series had such an electrocardiogram.

Type D (One Patient): In this type of pattern the process of ventricular activation is initiated at the base of the ventricular septum or near the bundle of His. The P-R interval is short because of early activation of ventricular depolarization but the QRS complex is only slightly, if at all, prolonged. The QRS complex is only minimally deformed since the order of ventricular depolarization is only slightly disturbed. This variant of the Wolff-Parkinson-White syndrome usually is difficult to identify unless normal conduction occurs from time to time, as was recorded in the one patient (7%) in this series.

Comment: It can be seen that in the majority of patients with the Wolff-Parkinson-White syndrome the initial process of ventricular activation is directed superiorly, to the left (Δ I positive, Δ III negative), and anteriorly (Δ V_2 positive). This situation is similar to infarction of the diaphrag-

matic surface of the heart. Thus, the QRS complex in the Wolff-Parkinson-White syndrome in some respects resembles posterior myocardial infarction. Furthermore, since the early process of ventricular depolarization is usually migrating from right to left the cavity of the left ventricle is positive at that time, so that in the event of left ventricular myocardial infarction the usual diagnostic Q waves are not recorded. Furthermore, S-T segment shifts are also frequently observed in the syndrome. Such situations as these make the electrocardiographic diagnosis of underlying myocardial disease difficult. For example, Kistin and Robb [15] described a patient with acute posterior myocardial infarction and intermittent Wolff-Parkinson-White syndrome. The diagnostic Q waves were evident when normal conduction existed but were absent during abnormal ventricular activation.[15]

The Spatial Vectorcardiogram

The spatial vectorcardiograms of the 15 patients with the Wolff-Parkinson-White syndrome were divided into two fairly uniform groups (Group I, seven patients; Group II, eight patients) based upon the spatial orientation of the delta portion of the QRS sÊ-loop.

Group I (Seven Patients): The delta portion of the QRS sÊ-loop in this group, readily identifiable by its slow inscription and marked distortion, was oriented superiorly, to the left and, in all but one instance, posteriorly (Figure 2). The delta component of the QRS sÊ-loop was directed pos-

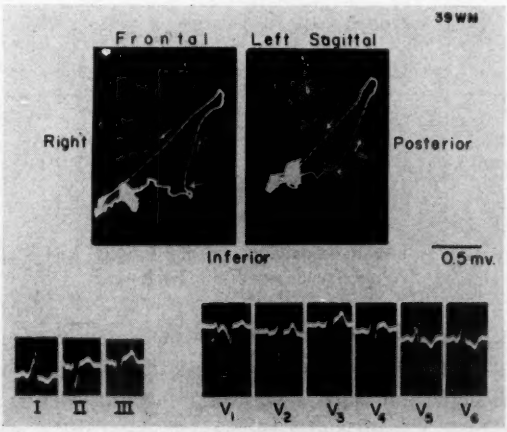

Fig. 2. Typical sVCG of patient in Group I. Note that the delta wave is distorted and slowly inscribed. The point at which the QRS sÊ-loop begins to rotate rapidly (horizontal arrow) represents the initiation of ventricular activation by the impulses entering the ventricles by way of the normal conduction tissue.

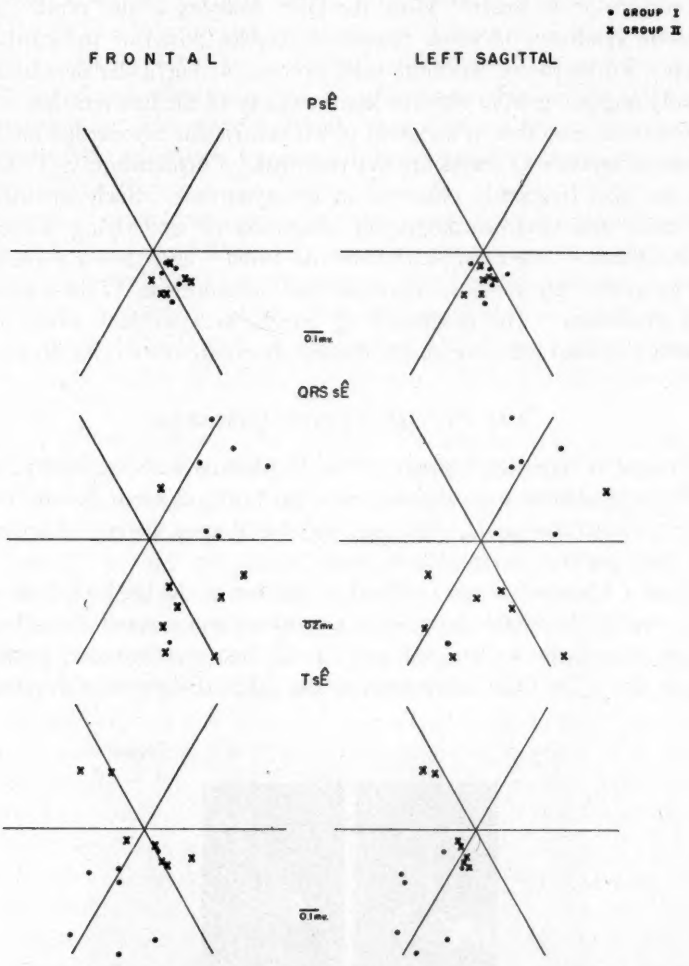

FIG. 3. Maximal mean instantaneous vectors of the P, QRS, and T sÊ-loops in the Wolff-Parkinson-White syndrome.

teriorly even in those patients in whom a positive delta wave was present in lead V_2 of the electrocardiogram. It is possible for the dipole source to be oriented (eccentric) in such a way that the projected force produces a positive deflection in a front and a back electrode at the same time. In the Wolff-Parkinson-White syndrome one would expect considerable eccentricity at least of the early vectors of ventricular activation (delta wave). In all but one instance the QRS sÊ-loop was also oriented superiorly, to the

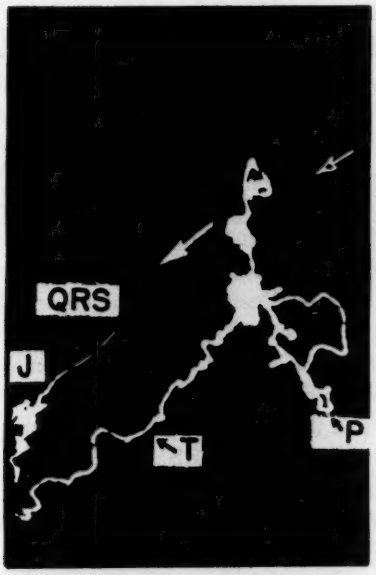

FIG. 4. Relationship of P, QRS, and T sÊ-loops in the same patient with Wolff-Parkinson-White syndrome as shown in Fig. 2.

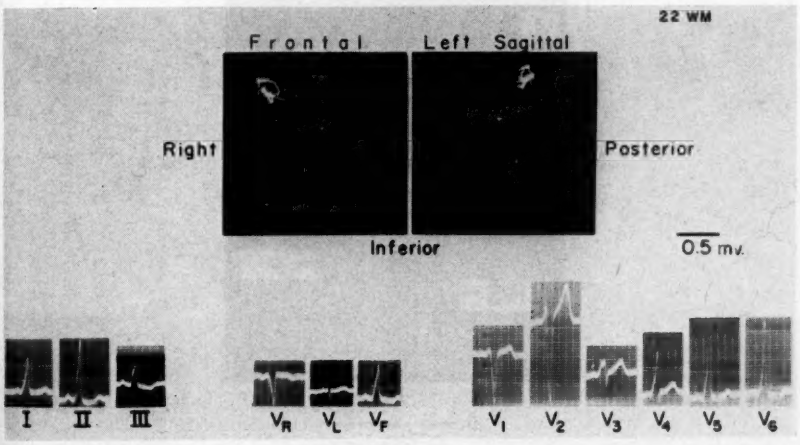

FIG. 5. Typical sVCG of patient in Group II. The delta wave is distorted and oriented inferiorly to the left. The horizontally oriented arrows indicate the termination of the delta portion of the QRS sÊ-loop.

left, and posteriorly—that is, it showed essentially the same spatial orientation as the delta portion of the QRS sÊ-loop (Figure 3).

The QRS sÊ-loop tended to be wide and elliptical and resembled that seen in left bundle branch block and in left ventricular hypertrophy. In three patients it was inscribed in a counterclockwise direction and in four patients in a clockwise direction in the frontal plane projection.

The T sÊ-loop was usually oriented to the right, inferiorly and anteriorly, i.e., in a direction opposite to that of the QRS sÊ-loop (Figure 3).

As expected by the displacement of the S-T segment of the electrocardiogram, the junction (J) was usually located superiorly, to the right, and anteriorly. This displacement of J provided a good opportunity to study the P sÊ-loop in detail since five of the seven patients in this group had P sÊ-loops which were inscribed clearly. The P sÊ-loop was oriented to the left, inferiorly, and near the 90° axis in most patients (Figure 3). Figure 4 shows the relationship of the P, QRS, and T sÊ-loops in the frontal plane projection.

Group II (Eight Patients): In all of the patients in this group the delta portion of the QRS sÊ-loop was oriented inferiorly and to the left in the

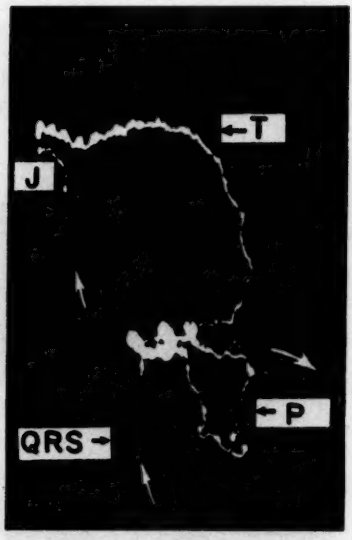

FIG. 6. Relationship of P, QRS, and T sÊ-loops in the same patient with Wolff-Parkinson-White syndrome as shown in Fig. 5.

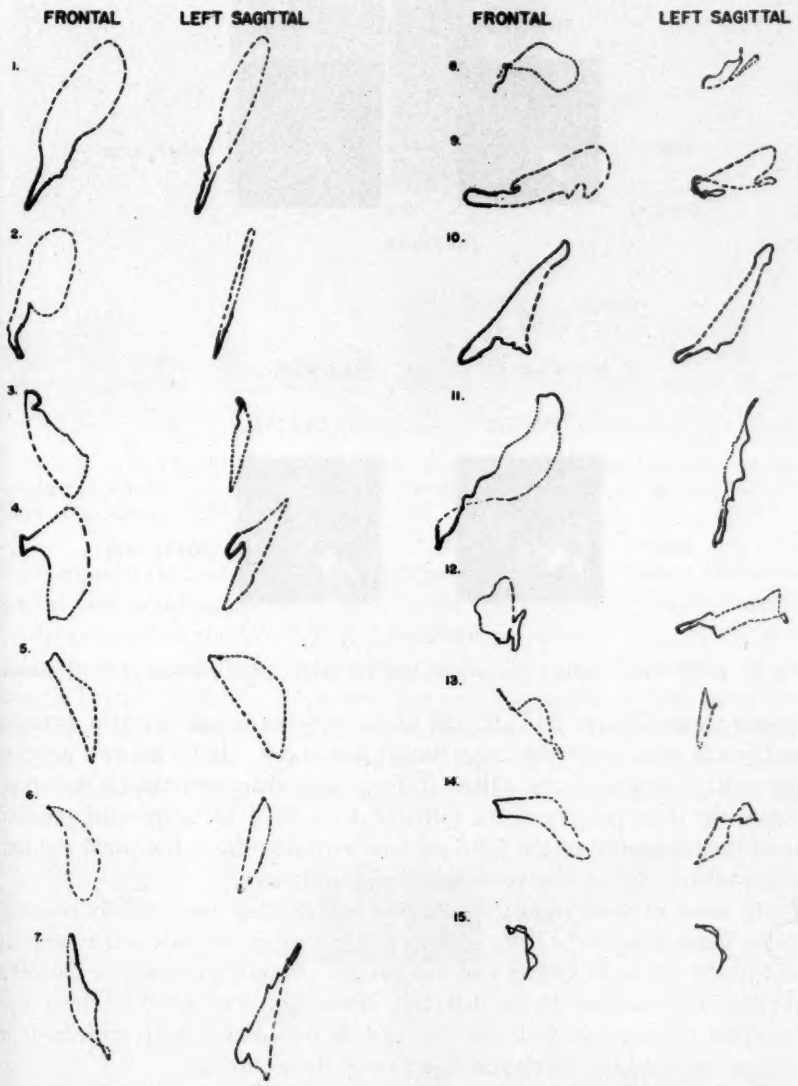

FIG. 7. Drawings of QRS sÊ-loops for the 15 patients with WPW syndrome. Patients 1-7 had no evidence of cardiac disease, whereas patients 8–15 had clinical evidence of heart disease as indicated in Table 1. See text for details.

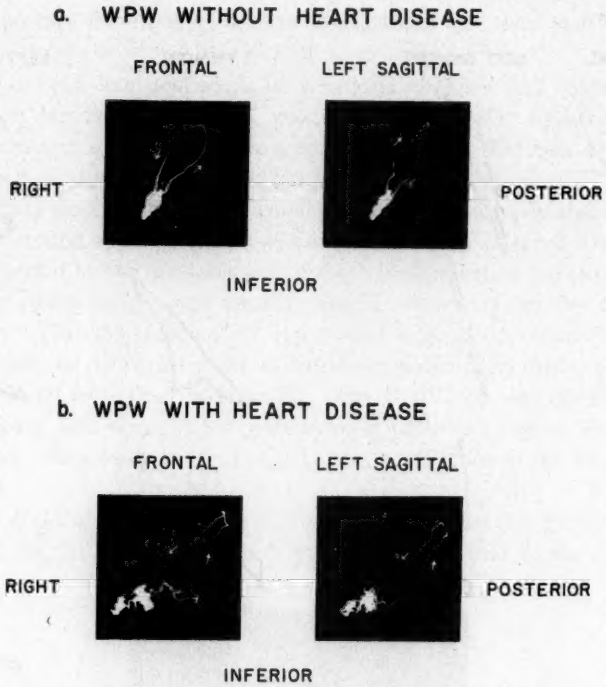

FIG. 8. sVCG from a patient (a) without and (b) with clinical evidence of heart disease.

frontal plane (Figure 5). In half of the patients it was oriented anterior and in half posterior to the isopotential point (i.p.). In all but two patients the delta portion of the QRS sÊ-loop was characteristically distorted. Again the delta portion of the QRS sÊ-loop could be easily distinguished from the component of the QRS sÊ-loop activated through normal conduction pathways by its distortion and slow inscription.

In seven of these eight patients the QRS sÊ-loop was spatially oriented in the same plane as the delta portion. However, it was oriented superiorly and to the left as in Group I in one patient (Figure 3), whereas the delta portion was oriented to the left and inferiorly. The QRS sÊ-loop was inscribed in a counterclockwise direction in the frontal plane projection in five patients and in a clockwise direction in three patients.

The T sÊ-loop was usually oriented inferiorly, to the left, and anteriorly, i.e., in the same direction as the QRS sÊ-loop (Figure 3).

The characteristics of the P sÊ-loop were similar to those described for Group I (Figure 3). Figure 6 shows the relationship of the QRS, T, and P sÊ-loops for the Group II patients.

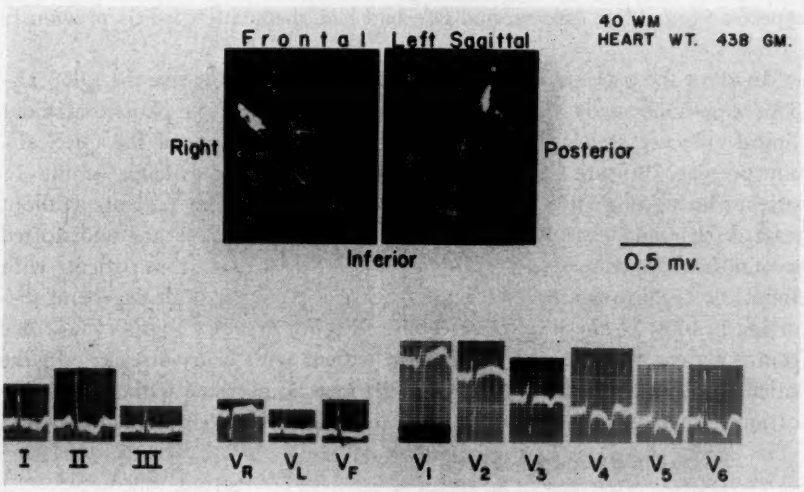

FIG. 9. sVCG and EKG of a patient with Wolff-Parkinson-White syndrome and basal myocardial infarction showing the marked reduction in magnitude of the late mean instantaneous vectors of the QRS $s\hat{E}$-loop.

Comment: It was considered important to determine whether or not the spatial vectorcardiogram could assist in the diagnosis of myocardial disease in the presence of the Wolff-Parkinson-White syndrome. The sVCG does assist in the recognition of myocardial infarction in the presence of left bundle branch block.[1, 2] Since only one of the patients in this series was autopsied, it was necessary to rely on clinical data for the diagnosis of heart disease. Eight of the 15 patients were considered to have clinical evidence of heart disease. Four patients had arteriosclerotic heart disease, two had

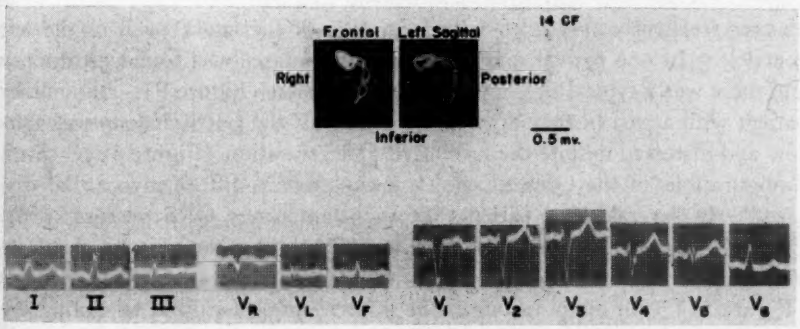

FIG. 10. sVCG and EKG of a patient with rheumatic carditis. Note the narrow distorted QRS $s\hat{E}$-loop.

hypertensive cardiac disease, and two had had rheumatic carditis previously (Table 1).

In all of the patients with clinical evidence of heart disease the QRS sÊ-loops were abnormally distorted, whereas in only one of the patients without clinical evidence of heart disease was abnormal distortion of the QRS sÊ-loop present. Figure 7 represents drawings of QRS sÊ-loops of the 15 patients included in this study. Loops 1 to 7 are from patients without heart disease and except for number 7 the QRS sÊ-loops are undistorted beyond the delta component. QRS sÊ-loops 8 to 15 are from patients with clinical or autopsy evidence of heart disease. Note the high degree of distortion in most of these QRS sÊ-loops. Figure 8 shows two sVCG's, one from a patient without and one from a patient with heart disease. In the patient without heart disease the QRS sÊ-loop is inscribed without any distortions, whereas in the patient with heart disease the loop is distorted in a

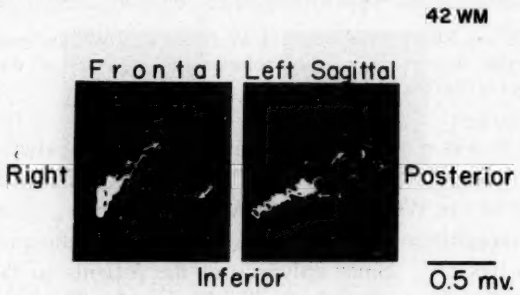

FIG. 11. sVCG of a patient with coronary artery disease. Note the distortion of the QRS sÊ-loop in the left sagittal plane projection. Such distortion is consistent with the loss of electrically active myocardial tissue.

manner frequently associated with infarction of the lateral wall of the left ventricle. In one patient a basal myocardial infarct was found at autopsy and there was a typical sVCG pattern of this lesion (Figure 9). In another patient with a past history of rheumatic carditis, the QRS sÊ-loop was narrow and distorted despite the prolonged QRS duration (Figure 10). Such configurations of the QRS sÊ-loop are common in diffuse myocardial disease.[20] In several other patients mean instantaneous QRS vectors of the QRS sÊ-loops were shortened, such as might be expected with death of localized portions of myocardium with associated loss of electric forces (Figure 11). In many instances the infarct can be localized by noting the time course of the shortened mean instantaneous vectors of the QRS sÊ-loop.

Because the initial phases of ventricular activation are abnormal, only

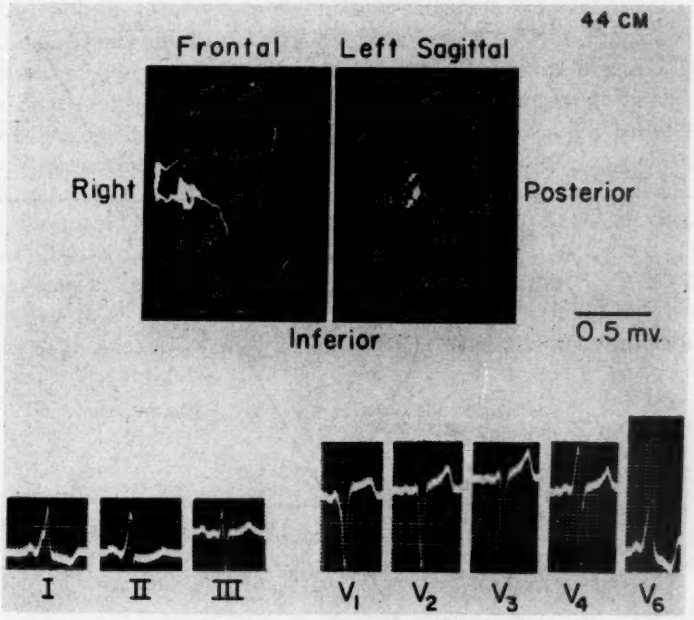

FIG. 12. sVCG and EKG of a patient with Wolff-Parkinson-White syndrome, Group II. The sVCG is compatible with septal myocardial infarction.

the portion of the QRS sÊ-loop beyond the delta portion appears to be reliable in the diagnosis and localization of myocardial infarction. For this reason and with the present state of knowledge, septal infarction is difficult to recognize from the sVCG in patients with the Wolff-Parkinson-White syndrome. In fact, because the septum does not participate in the initial process of ventricular activation, many of the sVCG's in patients with the syndrome resemble those of septal myocardial scarring (Figure 12). Nevertheless, many of the principles obtained from studies of the sVCG in LBBB can be applied to the sVCG in the Wolff-Parkinson-White syndrome to provide useful diagnostic information.

THE VENTRICULAR GRADIENT

The ventricular gradient was studied in the 15 patients with the Wolff-Parkinson-White syndrome to learn if the gradient could assist in the recogtion of cardiac disease in the presence of this syndrome.

$\hat{A}_{QRS}$ in the frontal plane was directed superiorly and to the left in six patients, inferiorly and to the left in eight patients, and inferiorly and to the right in one patient. $\hat{A}_T$ was located in the fifth and sixth sextants in

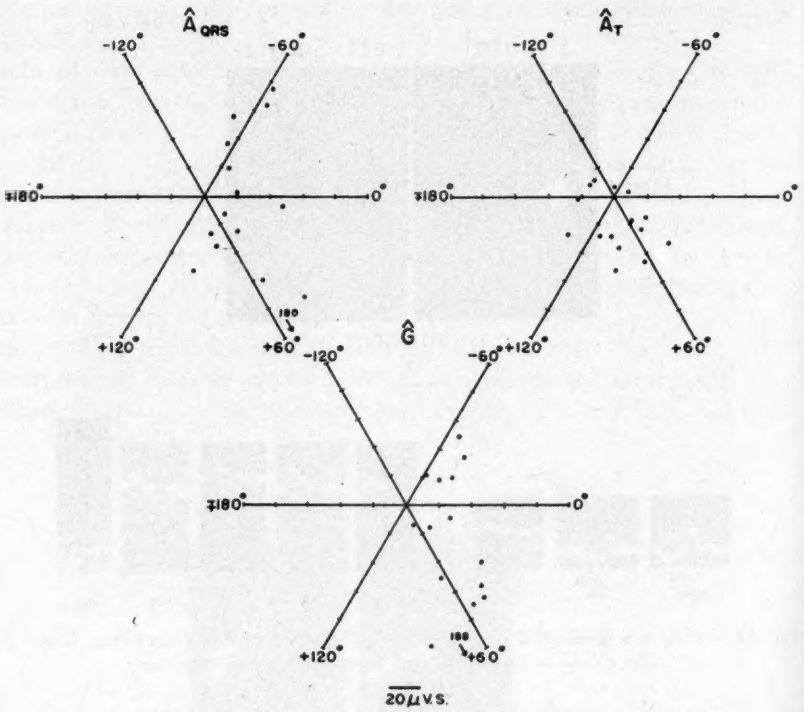

FIG. 13. $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ in the 15 patients with Wolff-Parkinson-White syndrome.

the frontal plane of the tri-axial reference system in most patients. In six patients, however, $\hat{A}_T$ was abnormally oriented (Figure 13).

The ventricular gradient was abnormal in eight patients. All but one patient with an abnormal $\hat{G}$ had clinical evidence of cardiac disease. The ventricular gradient was abnormally directed in six patients and abnormal

TABLE 2

The Distribution in Number of Patients of the Magnitude of the Angle Between $\hat{A}_{QRS}$ and $\hat{G}$, and $\hat{A}_T$ and $\hat{G}$

Position of $\hat{A}_{QRS}$ Relative to $\hat{G}$	Number of Patients	0°–35°	36°–70°	>70°	Mean $\hat{G}$:$\hat{A}_{QRS}$
Right	7	7	—	—	1.6
Left	8	7	—	1	0.9
Position of $\hat{A}_T$ Relative to $\hat{G}$					
Right	8	—	2	6	
Left	7	6	1	—	

in magnitude in three patients. In one patient $\hat{G}$ was abnormal in both direction and magnitude.

In seven patients the $\hat{G}:\hat{A}_{QRS}$ ratio was less than unity due to a decrease in the relative magnitude of $\hat{G}$ when $\hat{A}_{QRS}$ was directed superiorly and to the left, and $\hat{A}_T$ inferiorly and to the left (Table 2). The angle between $\hat{A}_{QRS}$ and $\hat{G}$ was normal in all but one patient, whereas in the majority of the patients the angle between $\hat{G}$ and $\hat{A}_T$ was abnormally wide (Table 2).

Comment: The ventricular gradient was helpful in suggesting myocardial disease in the presence of the pre-excitation syndrome. In the normal subject the T wave changes associated with the Wolff-Parkinson-White syndrome are secondary, so that the ventricular gradient should be normal. In one patient with an intermittent syndrome the $\hat{G}$ obtained for

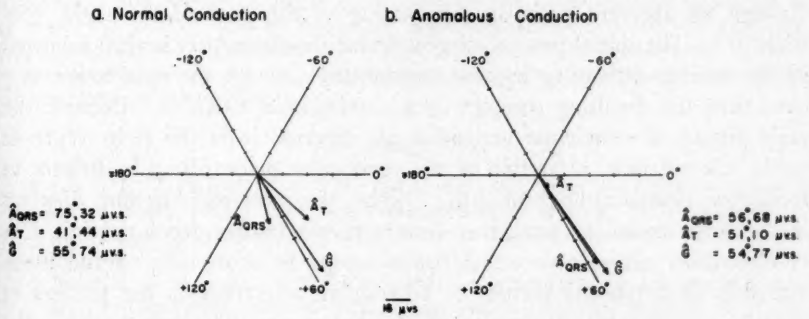

FIG. 14. $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ in a patient with intermittent Wolff-Parkinson-White syndrome. Note that there is essentially no change in $\hat{G}$ between the (a) normally conducted complex and the (b) anomalously conducted complex.

the pre-excitation complexes was essentially identical to that obtained when the pre-excitation state was absent (Figure 14). Berkun et al.[21] studied the spatial ventricular gradient in three patients who had the syndrome intermittently and found essentially no change in $\hat{G}$ between normal and Wolff-Parkinson-White complexes. In only one instance was an abnormal ventricular gradient obtained for a subject without detectable clinical evidence of cardiac disease. This patient was 38 years of age and may have had early coronary artery disease.

General Discussion

In the Wolff-Parkinson-White syndrome the process of ventricular activation is initiated by an impulse which enters the ventricular myocardium before the impulse through the normal conduction pathways

reaches the ventricles. The completed QRS complex or QRS sÊ-loop is composed, therefore, of at least two major phases of depolarization. The first phase, which results from early myocardial activation, is responsible for the delta wave. The second phase results from activation of the ventricular musculature by impulses which reach the ventricles by way of the normal conduction tissue. The various forms of the QRS complex are determined by the temporal relationships of these two major phases of depolarization, i.e., the delay in penetration of the normal impulse and the site of origin of the pre-excitation activation wave in the ventricles.

While it is recognized that many variations in the form of the QRS complex are possible, the most commonly encountered type of electrocardiographic pattern (as well as the one for which there is most careful postmortem study) is that which results from initial ventricular activation through an aberrant pathway terminating in the base of the right ventricle.[17-19] The initial process of ventricular depolarization is then followed by the normal activating impulse transmitted through the conduction system; thus the resulting complex is a *combination complex*. Because the early phases of ventricular activation are directed from the right ventricle to the left ventricle, infarction of the ventricular myocardium is difficult to recognize electrocardiographically. Since the vectorcardiogram displays in detail the mean instantaneous vectors of ventricular depolarization, loss of electrically active myocardial tissue results in shortening of the mean manifest instantaneous vectors of ventricular activation as the process of accession migrates in the vicinity of infarcted areas. This is reflected in the QRS sÊ-loop as a defect properly related temporally to the abnormal depolarization in the infarcted region of the heart.

The ventricular gradient may also be helpful in the diagnosis of myocardial disease in the presence of the Wolff-Parkinson-White syndrome since a normal myocardium is associated with a normal Ĝ. This study showed that the ventricular gradient may be helpful in the recognition of cardiac disease in the presence of the syndrome.

Summary

The electrocardiogram, spatial vectorcardiogram, and ventricular gradient were studied in 15 patients with pre-excitation (Wolff-Parkinson-White) syndrome to determine their usefulness in the recognition of myocardial disease in the presence of this disturbance. It was found that the spatial vectorcardiogram and ventricular gradient could suggest the diagnosis of myocardial disease in patients with this syndrome. These studies further indicate the value of the spatial vectorcardiogram in clinical cardiology.

Summario in Interlingua

Le diagnose electrocardiographic de morbo myocardial—particularmente de infarcimento myocardial—es difficile in le presentia de bloco de branca sinistre (BBS) o del syndrome de pre-excitation (syndrome WPW). Pro rationes theoric, le vectocardiogramma spatial (VCGs) pote devenir utile in le diagnose de morbo myocardial in le presentia del mentionate defectos de conduction. Un previe reporto ab iste laboratorio indicava que le VCGs esseva de adjuta in le diagnose de infarcimento myocardial in le presentia de BBS.

Le VCGs esseva registrate con le uso del systema de referentia tetrahedral equilateral in 15 patientes con le syndrome WPW. Septe del patientes esseva reguardate como clinicamente libere de morbo cardiac; le altere octo habeva varie typos de morbo cardiac. In omne le patientes sin morbo cardiac—con un exception—le VCGs non esseva distorquite, excepte que le portion initial (delta) del ansas sÊ de QRS esseva anormal. In omne le patientes con morbo cardiac, il esseva le configuration del ansas sÊ de QRS in ultra del portion delta que esseva anormal. In le majoritate del casos, le configurationes anormal esseva in congruentia con configurationes previemente describite como characteristic de morbo myocardial sin le syndrome de WPW. Con un exception, omne le patientes con anormal gradiente ventricular exhibiva signos clinic de morbo cardiac. Per consequente, le VCGs e le gradiente ventricular es utile in le diagnose de morbo myocardial in le presentia del syndrome de pre-excitation.

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A HEMODYNAMIC STUDY OF HYPERTENSION INCLUDING OBSERVATIONS ON CORONARY BLOOD FLOW * †

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Many studies of the systemic hemodynamics of arterial hypertension have been done, both in the experimental animal and in man, and these have recently been reviewed by Fries.[1] The specific data concerning cardiac output in man have been expanded and reviewed recently by Varnauskas [2] and by Taylor et al.[3] However, there is much less information available concerning coronary blood flow in hypertensive subjects.[4] The present study was done to add information concerning both systemic and coronary hemodynamics in subjects with both mild and severe hypertension.

Material and Methods

Twenty-one hypertensive subjects were studied by cardiac catheterization. These subjects were not decompensated, had not been sympathectomized, and were not receiving antihypertensive medication. Their cardiac output was determined by the Fick principle with a cardiac catheter placed in the pulmonary artery and a percutaneous needle placed in the femoral artery. Coronary blood flow was determined by the nitrous oxide saturation method. In some subjects, two intracardiac catheters were used simultaneously, one of which was placed in the pulmonary artery and the other in the coronary sinus; in other subjects, the catheter was withdrawn from the pulmonary artery subsequent to determination of cardiac output and placed in the coronary sinus prior to determination of the coronary blood flow. In all cases, the subjects were fasting and not sedated.

Independent of the results of cardiac catheterization, the subjects were grouped according to the Smithwick criteria,[5] and for purposes of statistical comparison (t-test), Group I, consisting of grades 1 and 2 subjects, was compared with Group II, comprised of subjects whose disease was graded

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TABLE 1

Cath. #	Age	Sex	Wt. Kg.	S.A. M^2	Card. Rate	Syst.[1] MABP	Pulm.[2] MABP	Min.[3] Vol. Resp.	O_2[4] Cons.	Body RQ	Art.[5] O_2	ΔA-[6] MVO_2	CSO_2[7]	ΔA[8] CSO_2	Art.[9] Hgb.	Art.[10] Hct.	Cardiac Index	LV[11] WI	RV[12] WI	Tot.[13] Per. Res.	Tot.[14] Pul. Res.	C[15] B F	CM[16] R O_2	C[17] R Q	C[18] V R
GROUP I																									
927	62	♂	63.0	1.78	77	126	18	6.0	136	0.77	16.1	2.5	5.1	12.0	14.7	44	5.4	9.3	1.3	1040	149	83	10.0	0.74	1.52
124	31	♂	75.5	1.88	93	123	10	9.4	143	1.16	20.3	4.4	6.1	14.2	15.5	47	3.3	5.4	0.4	1606	131	70	10.0	—	1.76
317	32	♀	69.8	1.76	101	134	15	5.2	131	0.75	19.4	3.9	7.3	11.5	15.0	47	3.4	6.2	0.7	1792	201	99	11.4	0.73	1.35
1050	46	♀	57.0	1.57	110	131	16	3.9	129	0.79	17.3	3.1	6.3	11.2	13.1	39	4.2	7.4	0.9	1599	195	141	15.8	0.79	1.08
1116	39	♂	87.0	2.02	79	137	18	7.0	180	0.74	17.9	3.3	4.8	12.8	14.0	42	5.4	10.1	1.3	995	131	86	11.0	0.73	1.59
288	57	♂	52.6	1.90	76	136	18	8.8	139	1.05	19.8	4.9	5.8	14.0	14.5	46	2.9	5.3	0.7	1988	265	50	6.8	0.94	2.74
176	47	♂	79.3	1.94	79	138	18	5.7	144	0.71	18.2	4.7	5.4	12.8	14.1	42	3.1	5.8	0.8	1852	242	76	9.7	0.57	1.82
214	35	♂	88.4	1.99	84	134	20	7.0	150	0.77	20.5	4.9	7.5	13.0	16.4	52	3.2	5.8	0.8	1749	258	65	8.4	0.84	2.13
1083	41	♂	73.0	1.87	67	144	20	5.9	163	0.70	17.5	3.8	6.3	10.9	13.8	46	4.3	8.4	1.2	1434	199	102	11.1	0.75	1.41
1074	41	♀	62.0	1.67	68	148	17	10.1	176	0.93	20.9	4.2	4.2	16.5	15.9	50	4.2	8.4	1.0	1690	194	66	10.9	0.78	2.24
976	39	♂	90.7	2.10	75	141	15	6.1	149	0.79	20.2	4.5	7.8	12.3	15.9	51	3.3	6.4	0.7	1620	172	92	11.3	0.80	1.53
1245	31	♀	52.0	1.52	87	155	15	4.2	156	0.75	16.2	3.3	4.2	11.1	12.2	39	4.7	10.0	1.0	1725	167	114	12.7	0.85	1.36
186	51	♀	53.0	1.45	76	159	13	3.9	139	0.72	17.9	4.3	3.6	14.3	13.5	42	3.2	7.0	0.6	2719	222	98	14.1	0.69	1.62
1024	37	♂	72.0	1.95	76	166	17	8.3	167	0.86	16.9	4.1	7.5	9.5	13.6	46	4.1	9.2	0.9	1671	171	115	10.9	0.93	1.44
Mean	42		70.0	1.81	82	141	16	6.5	150	0.82	18.5	4.0	5.9	12.6	14.4	45	3.9	7.5	0.9	1677	193	90	11.0	0.78	1.69
S.D.*	±10		±13	±.20	±12	±12	±3	±2.0	±16	±.14	±1.6	±.7	±1.4	±1.8	±1.2	±4	±0.8	±1.7	±.3	±409	±43	±24	±2.2	±.10	±.43
GROUP II																									
1096	59	♂	73.0	2.00	76	112	19	8.9	130	0.91	20.0	5.5	6.5	13.3	15.5	51	2.4	3.6	0.6	1894	321	67	8.9	0.68	1.66
178	63	♀	72.5	1.80	86	132	16	6.6	127	0.62	15.5	4.5	4.7	10.8	—	—	2.8	5.1	0.6	2078	252	79	8.6	0.62	1.67
219	31	♂	69.4	1.81	81	134	10	4.9	123	0.79	18.5	4.7	7.3	11.3	14.1	42	2.7	4.9	0.4	2240	166	68	8.8	0.69	1.99
265	46	♂	74.5	1.87	64	154	18	6.0	156	0.75	16.7	5.0	6.8	9.9	13.2	41	3.2	6.6	0.8	2092	245	67	6.6	0.79	2.30
1112	48	♀	66.0	1.75	82	160	17	4.6	109	0.74	14.3	4.4	3.2	10.7	11.3	38	2.5	5.4	0.6	2946	313	116	12.4	0.78	1.38
220	45	♂	58.9	1.70	86	170	22	6.1	142	0.82	18.5	5.8	6.6	11.9	13.9	45	2.5	5.8	0.7	3233	411	86	10.2	0.80	1.99
181	32	♀	57.0	1.63	99	173	8	5.9	139	0.73	19.3	5.2	3.6	15.7	14.2	42	2.7	6.3	0.3	3178	147	119	18.7	0.71	1.45
Mean	46		67.0	1.79	82	148	16	6.1	132	0.77	17.5	5.0	5.5	11.9	13.7	43	2.7	5.4	0.6	2523	265	86	10.6	0.72	1.78
S.D.*	±12		±7	±.12	±11	±23	±5	±1.4	±15	±.09	±2.1	±.5	±1.7	±2.0	±1.4	±4	±0.3	±1.0	±.2	±573	±92	±23	±4.0	± .07	±.33
30 NORMALS																									
Mean	28		67.0	1.77	79	93	16	5.2	137	0.80	17.2	3.6	5.7	11.6	13.6	43	3.9	4.9	0.8	1134	191	85	9.8	0.77	1.18
S.D.*	±6		±11	±.18	±10	±7	±3	±.8	±16	±.07	±1.5	±.5	±1.2	±1.5	±1.2	±3	±0.7	±0.9	±.2	±240	±48	±22	±23	±.06	±.32

* Standard deviation of the mean.

1. Systemic mean arterial blood pressure in mm. Hg.
2. Pulmonic mean arterial blood pressure in mm. Hg.
3. Minute volume of respiration in liters/minute.
4. Oxygen consumption, c.c. per minute per square meter body surface area.
5. Arterial oxygen content in c.c. per 100 ml. blood.
6. Arterial-mixed venous oxygen difference in c.c. per 100 ml. blood.
7. Coronary sinus blood oxygen content in ml. per 100 ml. of blood.
8. Arterial-coronary sinus blood oxygen difference in ml. per 100 ml. of blood.
9. Arterial hemoglobin in gm. per 100 ml. of blood.
10. Arterial hematocrit in per cent.
11. Left ventricular work in kilogram meters per minute per M^2 surface area.
12. Right ventricular work in kilogram meters per minute per M^2 surface area.
13. Total peripheral resistance in dynes $cm.^{-5}$ second.
14. Total pulmonary resistance in dynes $cm.^{-5}$ second.
15. Coronary blood flow in ml. per minute per 100 gm. of left ventricular myocardium.
16. Cardiac oxygen usage in ml. per 100 gm. of left ventricular myocardium per minute.
17. Cardiac respiratory quotient.
18. Coronary vascular resistance expressed in arbitrary units and obtained by dividing MABP by CBF.

as 3 and 4. Both groups of hypertensive subjects were also compared statistically with a group of normal subjects previously reported from this laboratory.[6]

Results

General Data: The basic data are presented in Tables 1 and 2 where it may be seen that the hypertensive subjects were considerably older (average age 43.5 years) than were the normals (average, 28 years). However, there was no significant difference between the ages of the two groups of hypertensive subjects (Group I averaged 42 years; Group II averaged 46 years). The mean arterial blood pressure of the hypertensive subjects was considerably higher than normal, this having been the criterion by which

Table 2

	Group I versus Normals		Group II versus Normals		Group I versus Group II	
	Δ%	P<	Δ%	P<	Δ%	P<
Age	+50.0	.001	+64.3	.001	+9.5	.5
Body surface area (M^2)	+2.3	.6	+1.1	.8	−1.1	.9
Heart rate	+3.8	.4	+3.8	.5	0.0	—
Mean art. blood press. (mm. Hg)	+51.6	.001	+59.1	.001	+5.0	.4
Mean pulm. art. blood press. (mm. Hg)	0.0	—	0.0	—	0.0	—
O_2 cons./M^2 body surface	+9.5	.02	−3.6	.5	−12.0	.05
Δ$A\text{-}VO_2$ (ml./100 ml. of blood)	+11.1	.05	+38.9	.001	+25.0	.01
CSO_2 (ml./100 ml. of blood)	+3.5	.7	−3.5	.8	−6.8	.6
Δ$A\text{-}CSO_2$ (ml./100 ml. of blood)	+8.6	.1	+2.6	.7	−5.6	.5
Cardiac index (L./min./M^2)	0.0	—	−30.8	.001	−30.8	.01
L. V. W. index (Kg. M/min./M^2)	+53.1	.001	+10.2	.3	−28.0	.01
R. V. W. index (Kg. M/min./M^2)	+12.5	.2	−25.0	.05	−33.3	.02
Total periph. resist. (cgs. units)	+47.9	.001	+122.5	.001	+50.4	.001
Total pulm. resist. (cgs. units)	+1.0	.9	+38.7	.01	+37.3	.05
Cor. blood flow (ml./100 gm. L. V. myocard./min.)	+5.9	.5	+1.2	—	−4.4	.8
$CMRO_2$ (ml. O_2/100 gm. myocard./min.)	+12.2	.2	+8.2	.5	−3.6	.8
Cardiac respiratory quotient	+1.3	.7	−6.5	.1	−8.3	.3
Cor. vas. resist.—units (MABP/CBF)	+43.2	.001	+50.8	.001	+5.3	.7

they were selected; there was, however, no significant difference in mean arterial pressure between Group I and Group II.

Systemic Hemodynamics: The cardiac index (cardiac output per square meter of body surface area) of the Group I hypertensive subjects was the same as that in the normals even though their oxygen consumption/M^2 surface areas was 9% higher. The reason for the higher oxygen consumption in Group I is not apparent although it is probable that a basal state is more difficult to achieve in labile hypertensive subjects, even though the procedure be the same in all subjects. The cardiac index in the Group II hypertensive subjects was significantly reduced. This reduction in cardiac output was reflected in the wider arteriovenous oxygen difference in the

subjects of Group II, since their body oxygen consumption was not significantly different from normal. Total peripheral resistance was elevated in Group I as compared to normal and in Group II as compared to Group I. Total pulmonary resistance was normal in Group I, but elevated in Group II, both as compared to normal and as compared to Group I. Left ventricular work was significantly elevated in Group I as compared to normal and as compared to Group II; however, in Group II the cardiac output was reduced sufficiently so that the left ventricular work was not significantly elevated and the right ventricular work index was significantly reduced. The pulmonary artery pressure was the same in the normals and in both groups of hypertensive subjects.

Coronary Hemodynamics: Coronary blood flow as measured per 100 gm. of left ventricular myocardium per minute did not differ significantly in either of the hypertensive groups when compared to the pooled series of normal males and females. Although the cardiac oxygen consumption per unit of weight was higher in the hypertensive subjects (especially those in Group I) than it was in the normals, the difference was variable and the change was not statistically significant. Coronary vascular resistance, on the other hand, was significantly elevated in both Group I and Group II hypertensive subjects.

Discussion

Blumgart and Weiss,[7] studying the velocity of blood flow in normals and in 18 hypertensive subjects by the "radium C method" (arm-to-arm circulation time), showed that subjects with arterial hypertension could be grouped into those with normal and those with prolonged circulation time. They found no evidence of congestive failure in the group of hypertensive subjects with prolonged circulation time, and set them apart from other subjects showing a prolonged circulation time in which a history of congestive failure seemed invariably to be present. In his monograph published in 1935, Gladstone reviewed much of the literature up to the time of his publication [8] and concluded that, although there were reports of both increased and decreased cardiac output in hypertensive subjects, the overall picture to that date indicated that cardiac output in hypertensive subjects was not elevated as compared to normal and hence the elevated arterial pressure of hypertensive subjects was due to an increase in peripheral vascular resistance. His own observations were made in 18 hypertensive subjects studied by the acetylene method, and from these he concluded that the cardiac output was normal. Bolomey et al.,[9] having studied 18 subjects using the direct Fick principle, concluded that the cardiac output was not significantly different from normal in hypertensive subjects.

Recent evidence, however, has accumulated which indicates that hypertensive subjects may be subdivided into two groups, one with normal and another with low cardiac output. The first of these studies, by Varnauskas,[2]

reported on 84 hypertensive subjects divided into two groups according to the criteria of the New York Heart Association. Varnauskas separated these groups into subgroups consisting of those who had determination of cardiac output alone and those who had simultaneous determination of cardiac output and renal blood flow, on the thesis that those who had the more complicated study might have a higher cardiac output. For comparison with the present study in which coronary blood flow and cardiac output were measured simultaneously, both groups from Varnauskas's study are added together on the assumption that determination of coronary flow may increase the cardiac output in the same manner as does the renal study. When this was done the first group contained 60 hypertensive subjects, graded 1 and 2, which were compared to the second group comprising 24 hypertensive subjects, graded 3 and 4. The cardiac index (direct Fick) in the first group averages 3.9 L./min., whereas the cardiac index in the second group averaged only 2.8 L./min. (significance of difference by t-test for non-paired values $= p < 0.001$). Similarly, prior to determination of cardiac output (direct Fick), Taylor et al.[3] divided a group of 20 hypertensive subjects into those who experienced dyspnea of considerable degree on exertion and those who had dyspnea of minor degree, and demonstrated that those with the greater disability had a lower cardiac output at rest and did not respond normally to exercise. It is emphasized that no patient in the study of Taylor et al.[3] or in the present group had any clinical evidence of right or left ventricular failure at the time of study. Two subjects in Taylor's group had suffered such episodes in the past, but were free of failure at the time of catheterization. No statement concerning the presence or absence of cardiac failure was found in the study by Varnauskas.

The present data confirm the studies by Varnauskas [2] and by Taylor et al.[3] It would seem that the discrepancy between these more recent observations and the results which have been reported previously is due to the fact that the present subjects have been grouped so that those with more advanced disease are separated from those with less advanced disease; hence a difference has been revealed which formerly was obscured by comparing all hypertensive subjects as a group with normotensive subjects. In view of the data by Brandfonbrener et al.,[10] which show a progressive decline in cardiac output with age, one may question the significance of the lower cardiac output in Group II of Taylor et al. (mean age Group I = 37 years; mean age Group II = 47 years). However, the difference in cardiac output seems excessive to attribute to only one more decade of life. Similar criticism seems much less applicable to Varnauskas's study since the respective mean ages for the comparable groups were 43 and 49 years, and to the present study where the mean age of Group I was 42 years and that of Group II was 46 years. It is interesting to speculate that the present division into those with normal cardiac output and those with reduced cardiac output represents the same groups as were originally separated by Blumgart and Weiss in 1927 [7] when

they divided hypertensive subjects into those with normal and those with prolonged circulation time.

The considerable elevation in total peripheral vascular resistance in hypertensive subjects is abundantly confirmed.[1, 4, 7, 8] It is of interest, however, that as the disease process advances, peripheral resistance continues to rise in association with decreasing cardiac output.[2, 3] In the more advanced form of the disease, grades 3 and 4, pulmonary vascular resistance is also elevated.[2, 3] In neither the greater nor the lesser circulation in the present study was this continuing increase in vascular resistance accompanied by a further increase in intravascular pressure, since the pulmonary arterial pressure remained normal throughout, and the systemic arterial pressure was no higher in Group II than in Group I of the hypertensive subjects. In the preceding studies [2, 3] pressure was higher in both the greater and lesser circuits of those with more advanced disease, and this may well depend on the stage to which the disease has advanced.

Coronary blood flow per 100 gm. of left ventricle was reported previously by Bing to be normal in seven hypertensive subjects [4] and this is confirmed in the present study. It is interesting to speculate that left ventricular hypertrophy is related directly to the increase in cardiac work and, therefore, the quantity of work done per unit of left ventricular mass remains the same even in the presence of hypertensive disease. If this were true, and the mass of the left ventricle were related directly to the increase in cardiac work, it may be equally true that cardiac efficiency is maintained in the Group I hypertensive subjects since the cardiac oxygen consumption per unit weight of the left ventricle is not significantly increased and left ventricular work is clearly increased. In the Group II hypertensive subjects, however, with reduced cardiac output and normal left ventricular work, it seems reasonable to conclude that cardiac efficiency is reduced, since their left ventricular hypertrophy was, if anything, more rather than less than that of the subjects in Group I. Cardiac efficiency cannot be expressed mathematically in the absence of specific knowledge of myocardial weight or a more accurate method of calculating cardiac work than with the Starling formula; hence discussion of efficiency is speculative in that the actual myocardial efficiency is not known. The increase in coronary vascular resistance in these hypertensive subjects is remarkable, as is the increase in their peripheral vascular resistance.

Conclusions

1. Hemodynamic data are presented for a series of 21 hypertensive subjects and these are compared with data from 30 normotensive subjects.

2. In the 14 subjects with Smithwick grades 1 and 2 hypertension (Group I), cardiac index was normal, whereas in the seven subjects with grades 3 and 4 hypertension (Group II), cardiac index was reduced.

3. Total peripheral vascular resistance was elevated in both groups of

hypertensive subjects and was significantly higher in Group II than in Group I. Total pulmonary resistance was elevated only in the Group II subjects.

4. The left ventricular work index was elevated in Group I hypertensive subjects, but normal in Group II. Right ventricular work index was normal in Group I but reduced in Group II.

5. Coronary blood flow was normal in both groups as was myocardial oxygen consumption per 100 gm.; however, coronary vascular resistance is significantly elevated in both groups of hypertensive subjects.

6. It is concluded that cardiac efficiency must be reduced in Group II, since myocardial oxygen consumption per unit of weight was normal, myocardial weight was high, and cardiac work was normal.

Summario in Interlingua

Es presentate datos hemodynamic pro un serie de 21 subjectos hypertensive in comparation con simile datos ab 30 subjectos normotensive.

In le 14 subjectos con hypertension de grados Smithwich 1 e 2 (Gruppo I) le indice cardiac esseva normal. In le 7 subjectos con hypertension de grados Smithwich 3 e 4 (Gruppo II) le indice cardiac esseva reducite.

Le total resistentia periphero-vascular esseva elevate in ambe le gruppos de subjectos hypertensive. Illo esseva significativemente plus alte in Gruppo II que in Gruppo I. Le total resistentia pulmonar esseva elevate solmente in subjectos del Gruppo II.

Le indice de travalio sinistro-ventricular esseva elevate in hypertensivos de Gruppo I. Illo esseva normal in hypertensivos de Gruppo II. Le indice de travalio dextero-ventricular esseva normal in Gruppo I e reducite in Gruppo II.

Le fluxo de sanguine coronari esseva normal in ambe gruppos. Le mesmo valeva pro le consumption de oxygeno per le myocardio calculate pro 100 g. Tamen, le resistentia coronari esseva significativemente elevate in ambe gruppos de subjectos hypertensive.

Es concludite que le efficacia cardiac esseva necessarimente reducite in Gruppo II, proque le consumption myocardial de oxygeno per unitate de peso esseva normal, le peso myocardial esseva elevate, e le travalio cardiac esseva normal.

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OBSERVATIONS ON SEASONAL VARIATIONS IN TOTAL SERUM CHOLESTEROL LEVEL AMONG HEALTHY YOUNG PRISONERS * †

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The total serum cholesterol level in a given individual at any particular point in time is the result of numerous technical and biologic variables.[1-5] § Many different methods of chemical analysis of the total cholesterol content of blood serum have been described and compared, both in terms of absolute values and of reproducibility; the technical aspects of cholesterol variability, however, do not concern us here. The biologic factors which influence the level of cholesterol are of even greater diversity and importance. The effects of age, sex, heredity, and diet have been well documented. In contrast, scant attention has been paid to the possibility of seasonal variations in cholesterol level.[5]

Our interest in seasonal fluctuations in cholesterol level stems from a long-term study of the precursors of hypertension and coronary artery disease using Johns Hopkins medical students as subjects.[6] In the course of the study, the effects of a number of factors on cholesterol level have been explored, and repeated determinations have been made on individual subjects at various intervals of time.[2, 4, 7] While some factors, such as heredity, are constant, others are much more variable in their influence on cholesterol level. Among the variable factors, we have studied the effects of academic stress on 52 first-year male medical students.[8] Significant differences in mean cholesterol levels were found between serum samples taken at the time of the final anatomy examinations in January (Test II) and at a less stressful time 13 to 105 days later (Test III). Similar differences were found between samples taken in October shortly after admission to medical school (Test I) and Test III. These findings were consistent with the hypothesis that stress such as that which accompanies the first few weeks of medical school or important final examinations is accompanied by a significant mean rise in cholesterol level. However, as we pointed out, these studies were not controlled as to possible seasonal variations acting independently of stress.

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Accordingly, we have measured the cholesterol levels of a group of healthy white male prisoners in the Maryland State Penitentiary at monthly intervals over the period of one year. The subjects were comparable to the medical students in age, sex, race, and geographic location, but they were not subject to such periodic *group* stresses as examinations, although each undoubtedly had his own private worries. In this way we hoped to obtain information which might throw additional light on the factors responsible for the variations in cholesterol level observed among medical students.

Method

Twenty-five prisoners in the Maryland State Penitentiary volunteered for the study. The penitentiary is located in Baltimore, Maryland, about a mile from the Johns Hopkins School of Medicine. Only white men in good health between the ages of 20 and 29 were eligible. The subjects were actually 22 to 28 years of age. One, subject 17, was a Mexican; none were of Jewish ancestry. Prisoners admitted to the penitentiary within a year or to be discharged within a year of the study were excluded in order to eliminate periods of potential stress. All subjects were still in the penitentiary six months after the termination of the study except for subject 15, who was unexpectedly paroled on February 8, 1960.

We planned to collect single serum samples on each subject at approximately monthly intervals over the period of one year. As it eventuated, cholesterol information was obtained on 14 occasions in a 12-month period beginning November, 1958 and ending in November, 1959. Blood was drawn twice in December, 1958 and once in every other month. An additional determination on December 23 provided extra information as to the effect of stress at the Christmas season. Serum was collected from seven prisoners on November 6, 1958, and from the remainder on November 13, 1958. These data are considered preliminary because, subsequently, blood was drawn from all subjects on the same day.

The venipunctures were made after breakfast between 9 and 11 a.m., and the blood taken immediately to the Clinical Chemistry Laboratory of the Johns Hopkins Hospital, where the serum was separated and frozen. Using the Buell adaptation of the Sackett modification of the Bloor method, the cholesterol determinations were carried out under fluorescent light in an air-conditioned laboratory.[2] The chemical analyses were made by the same two technicians throughout the study; they had also performed all the cholesterol determinations in a previously published study.[4] Accordingly, the prisoner studies are entirely comparable to the medical student studies in regard to chemical technic and reproducibility.

In addition to cholesterol levels, the following information was obtained in January and October on each prisoner by one of us (H. W. D. H.): height, weight, and, in the sitting position, blood pressure and heart rate. The prisoner's occupation and habits of smoking and exercise were recorded as well as his parents' smoking habits and medical histories. Electrocardio-

grams and teleoroentgenograms taken in November, 1958, were within normal limits in all the subjects.

Results

Table 1 presents all of the cholesterol data compiled from November 6, 1958 through November 12, 1959. The data for November, 1958, are considered preliminary and are not included in the analyses of seasonal effect. Of the 25 participating prisoners, 16 had complete cholesterol data recorded on each date from December 4, 1958, through November 12, 1959. They remained in good health throughout this experimental period. The data on these subjects (Group A) are entirely suitable for detailed study of a seasonal effect. In eight subjects (Group B) cholesterol determinations were missing on one or two occasions because of illness, disciplinary measures, or other reasons.* Because of these irregularities, the data on Group B are listed separately. One subject refused to cooperate after January, 1959. His individual data are presented in footnote *c*, but are not included in the group analyses. Subjects in Groups A and B were observed for a total period of from 365 to 372 days. Successive cholesterol determinations were done between 17 and 36 days apart for subjects in Group A, and between 17 and 66 days apart for subjects in Group B.

The subjects within both Groups A and B were divided according to their mean cholesterol levels for the total series (November, 1958, to November, 1959) into those with a mean of < 225 mg./100 ml. (low); 225–274 mg./100 ml. (intermediate); and $\geqq 275$ mg./100 ml. (high), as shown in columns 1 and 18. The prisoners represent a wide variety of cholesterol types with mean values per subject ranging from 167.1 mg./100 ml. (subject 17), to 307.6 mg./100 ml. (subject 16). When Groups A and B are considered jointly, individual values as low as 148 mg./ml. and as high as 387 mg./100 ml. were observed. The standard deviation, range, and size of range for the total series per subject are given in columns 19 to 21 of Table 1. The standard deviations run from a low of 10.8 mg./100 ml. to a high of 49.6 mg./100 ml., and the size of range from a low of 38 mg./ml. to a high of 150 mg./100 ml. As previously reported, the standard deviations are larger for the high mean cholesterol levels, but there is considerable variation within both the low and the intermediate cholesterol classifications.[2, 4]

Seasonal Effects

The data for each prisoner were first considered on an individual basis. It was apparent from a visual appraisal of 24 separate graphs, made from the data recorded in Table 1, that seasonal trends of a similar nature existed

* Subjects 22 and 24 were inadvertently included in an independent research study on vitamin B_{12} by another investigator and were given massive injections between June 19 and September 4.

TABLE 1—Individual Cholesterol Values

A. 16 Subjects with Complete Cholesterol Data

Cholesterol Group[a]	Subject No.	Preliminary Data, Nov. 1958		Data for Year December, 1958–November, 1959													Mean of All Serum Samples[a]	Standard Deviation	Range	Size of Range
		Nov. 6	Nov. 13	Dec. 4	Dec. 23	Jan. 8	Feb. 12	Mar. 3	Apr. 2	May 7	June 4	Ju y 2	Aug. 6	Sept. 4	Oct. 8	Nov. 12				
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)
I	1	160	—	186	180	178	193	186	193	*148*[b]	165	175	175	193	175	**205**[b]	179.4	15.0	148–205	57
Low <225 mg.	2	—	186	200	193	212	170	193	170	*148*	160	180	170	186	170	205	181.6	18.1	148–212	64
per 100 ml.	3	—	212	193	186	193	210	180	175	*170*	*170*	*170*	180	180	175	**278**	190.9	28.6	170–278	108
	4	—	200	212	**225**	205	180	200	218	193	200	180	193	193	*175*	**225**	199.9	16.0	175–225	50
	5	—	218	212	**240**	**240**	212	218	218	*175*	200	205	200	186	193	**240**	211.2	20.0	175–240	65
	6	—	205	233	**248**	205	212	225	233	193	205	225	212	240	*180*	233	217.8	19.2	180–248	68
	7	—	240	**255**	240	205	225	**255**	212	200	*170*	200	193	233	200	*225*	218.1	25.0	170–255	85
	8	—	205	**270**	212	248	218	225	*180*	200	218	205	218	255	193	225	219.4	24.5	180–270	90
II	9	—	212	255	240	263	233	255	205	233	205	*200*	218	263	205	**270**	232.6	25.3	200–270	70
Intermediate	10	—	233	**278**	263	263	*205*	225	233	218	225	225	*205*	218	248	233	233.7	21.9	205–278	73
225–274 mg. per	11	240	—	278	263	**315**	240	255	233	*225*	*225*	233	233	*225*	248	248	247.2	24.9	225–315	90
100 ml.	12	225	—	270	305	278	240	278	240	270	255	263	248	240	*233*	**315**	261.4	26.6	225–315	90
III	13	—	355	**365**	**375**	345	295	315	263	270	270	*225*	240	287	233	305	295.9	49.6	225–375	150
High ≥ 275 mg.	14	315	—	**375**	325	365	295	295	325	263	263	278	263	278	*233*	325	299.9	40.7	233–375	142
per 100 ml.	15	—	305	295	**387**	365	279	335	278	*248*	270	305	278	305	270	295	301.1	38.3	248–387	139
	16	278	—	**365**	278	355	345	355	295	278	263	*255*	295	295	325	325	307.6	36.8	255–365	110
Mean I	1–8	203.2		220.1	215.5	210.8	202.5	210.2	199.9	*178.4*	186.0	192.5	192.6	208.2	182.6	**229.5**	202.3		148–278	73.4
II	9–12	227.5		270.2	267.8	**279.8**	229.5	253.2	227.8	236.5	227.5	230.2	*226.0*	236 5	233.5	266.5	243.8		200–315	80.8
III	13–16	313.2		350.0	341.2	**357.5**	303.5	325.0	290.2	*264.8*	266.5	265.8	269.0	291.2	265.2	312.5	301.1		225–387	135,3
Grand Mean I, II & III	1–16	236.8		**265.1**	260.0	264.7	234.5	249.7	229.4	*214.5*	216.5	220.2	220.1	236.1	216.0	259.5	237.4		148–387	90.7

B. 8 Subjects with Incomplete Cholesterol Data[c]

I	17	148	—	180	170	**186**	*154*	160	175	*154*	165	170	—	170	170	170	167.1	10.8	148–186	38
Low <225 mg.	18	—	186	200	200	212	200	160	205	180	186	193	—	205	*154*	**233**	193.4	21.0	154–233	79
per 100 ml.	19	175	—	210	200	**225**	180	180	200	—	186	186	—	212	*170*	**225**	195.8	19.1	170–225	55
	20	—	212	218	**260**	225	200	240	218	205	212	205	—	225	*170*	218	216.0	21.1	170–260	90
	21	—	200	**270**	218	225	200	255	—	*186*	212	212	218	200	212	233	218.5	23.2	186–270	84
II	22	—	218	218	270	263	*180*	218	255	240	**295**	212	—	205	225	—	233.2	32.2	180–295	115
Intermediate	23	—	233	255	*225*	*225*	248	255	255	233	233	240	—	255	*225*	**263**	241.9	13.7	225–263	38
225–274 mg. per	24	—	255	233	240	263	—	**278**	263	240	270	*200*	—	225	240	**278**	248.8	23.4	200–278	78
100 ml.																				
Mean I & II[d]	17–24	203.4		223.0	222.9	**228.0**	—	218.2	—	—	219.9	202.2	—	212.1	*195.8*	—	214.3[e]		148–295	72.1
Grand Mean[d]	1–24	225.7		251.1	247.6	**252.5**	—	239.2	—	—	217.6	214.2	—	228.1	*209.2*	—	229.7[e]		148–387	84.5

[a] The mean cholesterol per subject for the total series of determinations, from Nov. 1958 through Nov. 1959, is the basis for the classification of subjects into low, intermediate, and high cholesterol groups (see column 18). N = 14 for Group A and 13 for Group B, except for subjects 19, 22 and 24, for whom N = 12.

[b] Extreme cholesterol values for period Dec. 4, 1958–Nov. 12, 1959, inclusive, are indicated by bold-faced type (maximal) and italics (minimal).

[c] Subject 25 is not included because he dropped out after four determinations: Nov. 13, 1958, 225; Dec. 4, 255; Dec. 23, 255; and Jan. 8, 1959, 255 mg. per 100 ml.

[d] Means are given at each date where data are complete for all subjects in the groups considered.

[e] Vertical mean.

among many of the subjects. Higher cholesterol values tended to prevail in December of 1958, and in January and November of 1959. Lower cholesterol values were more prevalent in warmer months (Figure 1).

Table 1 shows the dates of the maximal and minimal cholesterol values observed in each subject's record within the period December 4, 1958, to November 12, 1959. In several subjects the maximal or minimal values were encountered on two or three occasions. Among the 16 subjects of Group A, for whom we have a symmetric array of 13 cholesterol determinations per subject, a maximal cholesterol value came either in December or January for 12 subjects, and in November for the other four subjects. The

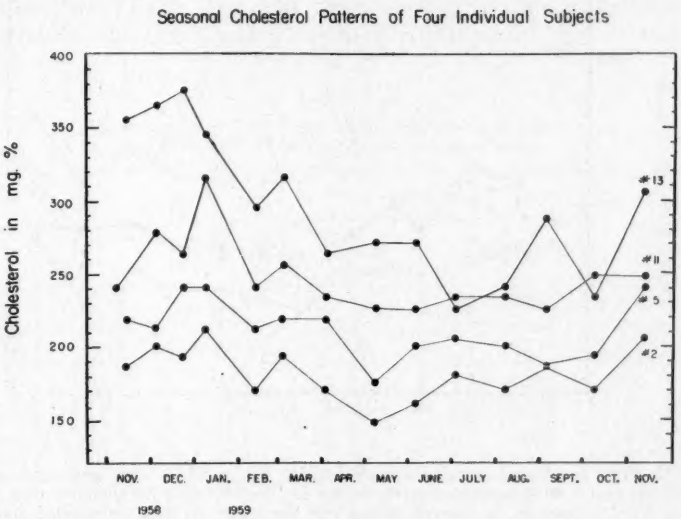

FIG. 1. The pattern of seasonal cholesterol variation exhibited by four individual prisoners observed monthly over the period of a year. All 14 cholesterol values have been charted for subject 13 (high cholesterol type), subjects 11 and 5 (intermediate cholesterol type), and subject 2 (low cholesterol type). The exact values and dates are shown in Table 1, Group A. An extra determination was obtained on December 23 (see text).

cholesterol levels of the eight subjects in Group B, whose data are less complete, showed a similar pattern; for seven of these eight prisoners a maximal cholesterol value came either in December, January, or November.

Examination of the individual records of the subjects in Group A showed that May, June, July, and October were the months with a minimal value for 14 of 16 subjects. Seven of eight subjects in Group B had a minimal value in the same four months. Of the 24 subjects, all but subjects 22 and 23 showed varying degrees of seasonal cholesterol fluctuation. In some, the seasonal effect was relatively small (subject 1) while in others it was considerable (subject 14). In some, the high cholesterol values were more

* Vertical mean.

prominent in the December–January period (subject 11); in others, in the following November (subject 3).

Detailed examination of the mean monthly cholesterol values for the 16 subjects in Group A shows an interesting seasonal pattern (Figure 2). There was a high plateau during December and January, a decline between January and February, and an upward trend between February and March. This is followed by a sharp decline from March to May, when the lowest point of the year is reached. The low level is fairly stable and well main-

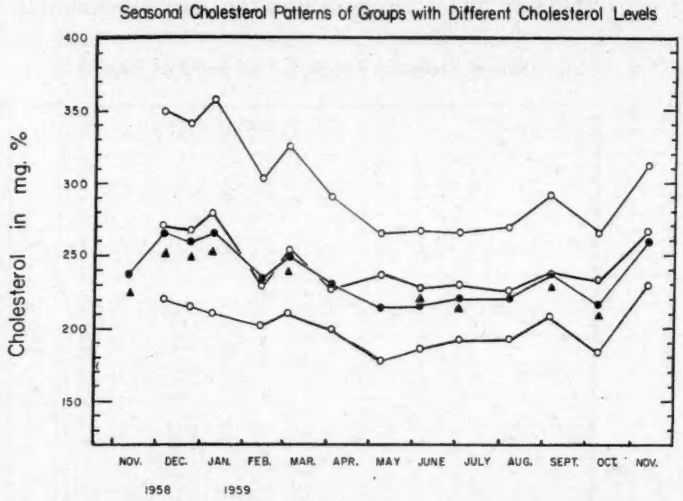

FIG. 2. The mean cholesterol levels of healthy young white male prisoners over the period of one year. ● = mean cholesterol values for the 16 men with complete data (Group A, Table 1). ○ = mean cholesterol values for the same 16 men subdivided into three groups according to mean cholesterol level as in Table 1. I. Low: 8 men with levels below 225 mg. per 100 ml. II. Intermediate: 4 men with levels of 225–274 mg. per 100 ml. III. High: 4 men with levels of 275 mg. per 100 ml. or over. ▲ = mean cholesterol values for 24 men (Table 1, Groups A and B) on the eight dates when all had cholesterol data. For purposes of graphic presentation, the cholesterol levels obtained on Nov. 6 and 13, 1958, have been pooled and are charted as a single dot or triangle half-way between those two dates.

tained during June, July, and August. A rise takes place between August and September, followed by a fall from September to October to a level like that of May through August, with another sharp rise between October and November. In November, 1959, the high winter level was again attained by the group as a whole, although the values for Group III had not yet risen to their December, 1958, level. On the other hand, in the preliminary observations made in November, 1958, none of the groups had reached the December level, suggesting that November is a transition month which varies somewhat from year to year. The seasonal trend was found among

low, intermediate, and high cholesterol types, whether subjects were considered individually or in groups (Figures 1 and 2). It will be seen that the pattern for the mean trend lines for groups is similar to those observed in individuals.

Further studies were carried out on the cholesterol data of the 24 subjects (Groups A + B, Table 1) on each of the eight dates on which information was complete for the entire group. Statistical analysis was limited to these eight dates in order to avoid introducing bias through omission. The mean values for the 24 subjects on these dates closely followed the pattern for the 16 subjects of Group A (Figure 2). The mean cholesterol values for the eight dates were compared two at a time by means of t tests for paired data (Table 2). The mean cholesterol values for December 4, December 23, and January 8 were significantly higher than the

TABLE 2

Comparison of Cholesterol Values for the Eight Dates on Which All 24 Subjects Had Complete Data

	Date[a] Comparison		For the 24 Differences			P Value[b]
			Absolute Mean Difference	Number of Positive Differences	Range of Differences	
	Jan. 8	Oct. 8	43.2	23	0 +132	<.001
	Dec. 4	Oct. 8	41.8	22	−7 +142	<.001
	Dec. 23	Oct. 8	38.4	20	−47 +142	<.001
	Jan. 8	July 2	38.2	22	−20 +120	<.001
	Dec. 4	July 2	36.8	23	−10 +140	<.001
A.	Jan. 8	June 4	34.8	20	−32 +102	<.001
	Dec. 4	June 4	33.5	22	−77 +112	<.001
	Dec. 23	July 2	33.4	22	−15 +150	<.001
	Mar. 3	Oct. 8	30.0	21	−23 +82	<.001
	Dec. 23	June 4	30.0	20	−30 +117	<.001
	Mar. 3	July 2	25.0	19	−33 +100	<.001
	Jan. 8	Sept. 4	24.4	17	−35 +90	.001<P<.01
	Dec. 4	Sept. 4	23.0	16	−10 +97	.001<P<.01
	Mar. 3	June 4	21.6	18	−77 +92	.001<P<.01
B.	Dec. 23	Sept. 4	19.5	16	−43 +88	.01<P<.02
	Sept. 4	Oct. 8	18.8	16	−30 +62	.001<P<.01
	July 2	Sept. 4	13.8	6	−63 +23	.001<P<.01
	Jan. 8	Mar. 3	13.2	15	−50 +70	.02<P<.05
	Dec. 4	Mar. 3	11.9	14	−45 +80	>.05
	Mar. 3	Sept. 4	11.1	15	−45 +60	>.05
	June 4	Sept. 4	10.5	7	−63 +90	>.05
	Dec. 23	Mar. 3	8.4	15	−77 +60	>.05
C.	June 4	Oct. 8	8.4	13	−62 +70	<.05
	July 2	Oct. 8	5.0	12	−70 +45	>.05
	Dec. 23	Jan. 8	4.8	9	−77 +43	>.05
	Dec. 4	Dec. 23	3.5	14	−92 +87	>.05
	June 4	July 2	3.4	8	−35 +83	>.05
	Dec. 4	Jan. 8	1.4	11	−70 +50	>.05

[a] For each subject, the cholesterol value for the second date in this column was subtracted from that for the first date to determine the algebraic magnitude of the difference.

[b] Results of t tests for paired data comparing the absolute mean difference with zero.

mean values for June 4, July 2 and October 8, respectively ($P < .001$). An average fall of from 38 to 43 mg./100 ml. occurred between the three December–January dates and October 8, with values for individual subjects dropping as much as 142 mg./100 ml., and with values for as many as 20 to 23 of the 24 subjects showing a fall. The mean cholesterol value for March 3 was also significantly higher than that for July 2 and October 8 ($P < .001$). The largest individual fall observed was 150 mg./100 ml.; this occurred between December 23 and July 2. When comparing mean cholesterol values on two dates, all absolute mean differences of 25 mg./100 ml. or more produced highly statistically significant results with $P < .001$. Other date comparisons of lesser orders of statistical significance are itemized in Table 2 (B). It is noteworthy that the mean cholesterol values for December 4, December 23, and January 8 are significantly different from the mean value for September. Of the remaining comparisons set forth in Table 2 (C), none is statistically significant.

Factors Which Might Have a Seasonal Influence on Cholesterol Level

Stress: Unlike medical students taking a final examination or tax accountants working against a deadline, the prisoners in this experiment, with one possible exception, were not subjected to any external situational stress which affected them all *as a group* at a single point in time. It is well recognized that holidays and anniversaries may have a disturbing effect. In the so-called "anniversary reaction," the arousal of memories on a birthday, a holiday, or the anniversary of a death in the family is reported to have such a stressful effect that an exacerbation of an underlying disease process, such as an attack of coronary thrombosis, may result.[9, 10] Of all the days in the year, Christmas probably has the greatest emotional impact on the most prisoners. Accordingly, an additional serum sample was obtained on December 23 for comparison with samples drawn on December 4 and on January 8. No transitory peak of cholesterol level occurred on December 23 to indicate the effect of excitement or emotionally disturbing thoughts during the days immediately before Christmas (Table 1 and Figure 2). The mean values for December 4, December 23, and January 8 were similarly high in all groups and in no instance was the December 23 value the highest. From our findings, it is not impossible to suppose that thoughts of Christmas beginning in November and continuing through December and early January produce a sustained emotional stress sufficient to raise cholesterol levels significantly, but this concept is only hypothetical.

Physical Activity: We have attempted to appraise the amount of physical activity involved in the occupation and recreational program of each subject (Table 4). All 24 men were employed within the institution six hours a day, five days a week throughout the entire year. Most subjects worked in a prison shop: print shop, shoe shop, sewing shop, metal shop, woodwork

shop, or barber shop. For the most part, these shop workers were arbitrarily rated as having jobs involving moderate physical activity; only two had jobs entailing heavy exertion. Seven worked as clerks, teachers, or librarians and were classified as having occupations involving light physical activity. The job activity of the prisoners does not seem to be associated with their cholesterol classification.

Although an increased amount of outdoor activity is available to penitentiary inmates during the warmer months, only seven of our subjects took appreciably more exercise in summer than in winter, according to their own statements and that of the recreation director of the penitentiary. Five subjects took no formal exercise at any season of the year. Twelve subjects

TABLE 3

Age, Height, Weight, Blood Pressure, and Heart Rate of All 24 Subjects by Mean Cholesterol Level at Two Times of Year

Cholesterol Group[a]	Subject Number[b]	Mean Cholesterol Level[c]	Age	Height		Weight		Systolic Pressure		Diastolic Pressure		Heart Rate	
				Jan.	Oct.	Jan.	Oct.	Jan.	Oct.	Jan.	Oct.	Jan.	Oct.
I Low	17	167.1	25	66	66	121	132	124	115	60	58	84	96
	1	179.4	25	69	70	136	150	130	126	88	72	80	84
	2	181.6	28	70	69	143	150	120	122	62	58	82	66
	3	190.9	26	72	74	218	190	120	125	70	70	62	60
	18	193.4	26	68	68	140	150	110	115	86	58	80	75
	19	195.8	23	68	68	136	139	125	136	65	62	90	96
	4	199.9	22	72	74	159	165	118	105	74	55	100	72
	5	211.2	25	69	69	165	169	112	115	60	58	72	76
	20	216.0	28	69	69	170	183	120	132	60	68	75	96
	6	217.8	27	71	70	148	141	115	108	65	55	99	81
	7	218.1	26	68	67	150	149	138	128	80	58	104	90
	21	218.5	27	71	72	171	173	105	118	62	62	96	102
	8	219.4	24	72	72	147	145	120	120	90	58	72	69
II Intermediate	9	232.6	26	64	64	116	117	124	110	78	60	86	88
	22	233.2	25	71	72	194	205	120	125	80	78	96	84
	10	233.7	25	72	74	195	195	130	128	86	58	76	86
	23	241.9	28	68	69	153	163	118	142	62	85	86	80
	11	247.2	28	65	65	137	134	128	128	72	52	130	114
	24	248.8	26	72	74	162	150	118	138	78	58	84	108
	12	261.4	27	72	72	167	163	120	130	78	60	70	78
III High	13	295.9	24	61	62	172	162	142	118	92	78	100	114
	14	299.9	28	66	66	145	150	118	122	70	60	74	69
	15	301.1	28	69	70	149	150	112	115	84	60	80	78
	16	307.6	27	67	67	168	178	110	135	96	94	82	75
Mean I		200.7	25.5	69.6	69.8	154.2	156.6	119.8	120.4	70.9	60.9	84.3	81.8
Mean II		242.7	26.4	69.1	70.0	160.6	161.0	122.6	128.7	76.3	64.4	89.7	91.1
Mean III		301.1	26.8	65.8	66.2	158.5	160.0	120.5	122.5	85.5	73.0	84.0	84.0
Grand mean		229.7	26.0	68.8	69.3	156.8	158.5	120.7	123.2	74.9	64.0	85.8	84.9

[a] As in Table 1.
[b] Subjects in Parts A and B of Table 1 have been intermingled according to mean cholesterol level because the data presented here are complete for all subjects.
[c] As in Table 1, column 18.

took regular exercise the year around. Each subject has been rated in Table 4 according to the type and amount of exercise taken.

Comparison of the exercise habits of the prisoners with their cholesterol levels shows that the mean of the cholesterol levels of the four men who took heavy exercise summer and winter was 212.8 mg./100 ml., and the mean for the eight subjects who had moderate physical activity the year around was 208.7 mg./100 ml. In contrast, the mean of the cholesterol levels of the five men who were entirely inactive throughout the year was 271.7

TABLE 4

Relationship of Mean Cholesterol Level and Standard Deviation to Smoking Habits, Amount of Physical Activity, and Parental History

Cholesterol Group[a]	Subject No.[b]	Mean Chol. Level	Standard Deviation	Job[c]	Exercise Habits[d]		Smoking Habits			Parental History[g]	Parental Smoking Habits[h]	
					Winter	Summer	Kind[e]	Years Smoked	Daily Amt.[f]		Father	Mother
	17	167.1	10.8	2	2	2	A	18	1	1	R	N
	1	179.4	15.0	2	1	1	B/C	9	2/2	3	F	N
	2	181.6	18.1	1	2	2	A	16	3	3	R	N
	3	190.9	28.6	2	3	3	C	5	1	3	R	N
	18	193.4	21.0	2	1−	1−	N	0	0	3	R	N
	19	195.8	19.1	2	2	2	A	8	2	1	R	N
I Low	4	199.9	16.0	2	3	3	A	9	2	3	R	L
	5	211.2	20.0	2	2	2	A	13	3	2	U	U
	20	216.0	21.1	2	0	2	A	4[i]	3	1	R	R
	6	217.8	19.2	1/2/3	1	2	A	3	3	1	R	R
	7	218.1	25.0	1/2	1	2	A	11	3	2	R	N
	21	218.5	23.2	1	3	3	A	12	2	1	R	?
	8	219.4	24.5	2	1	2	C	4	2	3	R	N
	9	232.6	25.3	2	0	1	A	13	3	3	R	?
	22	233.2	32.2	3	2	2	A	12	3	2	R	N
II	10	233.7	21.9	1	0	1	A	9	3	1	R	N
Inter-	23	241.9	13.7	2	3	3	A	15	3	1	R	?
mediate	11	247.2	24.9	3	0	0	A	13	1	3	R	N
	24	248.8	23.4	1	0	0	A	11	3	1	R	R
	12	261.4	26.6	2	0	0	B	10	3	3	R	R
	13	295.9	49.6	2	1	2	C	9	1	2	F	L
III	14	299.9	40.7	2	0	0	A	21[i]	3	3	R	N
High	15	301.1	38.3	2	0	0	A	13	3	2	U	?
	16	307.6	36.8	1/2	2	2	A	12	3	2	R	R

[a] As in Table 1.
[b] As in Table 3.
[c] Job: 1 = light; 2 = moderate; 3 = heavy physical activity.
[d] Exercise: 0 = none, 1, 2, and 3 as in *c* above.
[e] Kind: A = cigarettes; B = pipes; C = cigars; N = nonsmoker.
[f]

Amount:	Cigarettes	Pipes	Cigars
1 = light	1–10	—	1-2
2 = moderate	11–19	8–10	3–4
3 = heavy	20–40	25	—

[g] Parental history of hypertension and/or coronary disease: 1 = present in one or both parents; 2 = uncertain in one or both parents; 3 = absent in both parents.
[h] Parental smoking habits: N = nonsmoker; L = occasional smoker; R = regular smoker; F = former smoker; U = unknown to subject; ? = unspecified.
[i] Stopped smoking a year ago.

mg./100 ml., while the mean for the seven subjects who had more physical activity in spring and summer than in winter was 233.4 mg./100 ml. Thus, there was a gradation in mean cholesterol level among the prisoners grouped according to the amount of exercise taken during the year, with the inactive group having the highest and the groups with year around physical activity the lowest mean values respectively. The level for the group which was more active in summer than in winter was intermediate.

The relationship between exercise and cholesterol level has been somewhat controversial.[11, 12] While our findings suggest that exercise lowers cholesterol level, there was no clear relationship between seasonal changes in cholesterol level and in physical activity. Some of the best illustrations of a seasonal cholesterol pattern (e.g., subjects 2, 3, 5, 11, 12, 14, 15, and 19) are to be noted in those whose exercise habits remained constant throughout

TABLE 5

Monthly Quantities of Fats and Meats Purchased by Maryland State Penitentiary

Month Purchased	Lard (lbs.)	Oleomargarine (lbs.)	Salad Oil (gals.)	Fresh Pork (lbs.)	Total Meat (lbs.)
1958					
November	4,000	1,000	5	3,842	19,097
December	4,000	1,000	10	4,141	23,985
1959					
January	4,000	1,000	0	4,429	20,271
February	4,000	1,200	0	4,312	20,597
March	4,000	1,200	0	4,139	23,130
April	2,500	1,200	0	4,164	20,271
May	4,000	1,000	5	4,210	18,255
June	0	1,200	5	1,200	19,748
July	2,000	1,200	0	2,000	22,390
August	3,000	1,200	0	1,600	20,387
September	4,000	1,200	0	2,000	25,700
October	4,000	1,200	0	4,060	20,375

the year, regardless of the total amount of exercise taken (Table 1). Subject 20, who had the most pronounced seasonal change in activity, showed a seasonal cholesterol pattern which was in no way unusual. Thus, no parallel was found between seasonal cholesterol changes and the amount of or change in physical activity.

Dietary Fat: The institutional diet is as varied as the budgetary allowance, the eating habits of the inmates, and the ingenuity of the steward permit. The preponderance of Negro prisoners had a significant effect upon the menu. Fried foods and pork products were popular among the Negro inmates, while salad was not. The quantities of certain fats and meat products purchased each month during the year of the study are shown in Table 5.* These figures may provide an indirect measure of the amount of fat in

* Other fat-containing foods for which monthly estimates were not obtained: eggs, cheese, milk, seafoods, and vegetable shortening (used only in baking cake).

the prisoners' diet. Less lard was purchased during April, June, July, and August, less fresh pork during June, July, August, and September, and the least total meat for the year was purchased in May. It appears that less fat from these sources was consumed by the prison population as a whole between April and September. These months tend to parallel the period in which lower cholesterol levels were found. Comparison of sample menus selected at random for the week of June 28, 1959, and the week of November 8, 1959, on the other hand, showed no difference in the fat content of the diet. Calculated on the basis of average servings, dietary fat per day was 92 grams in June and 88 grams in November. Since we have no information concerning individual fat consumption by our white subjects, who may have rejected parts of the meals offered, further menu analysis was not carried out. Under these circumstances, it is difficult to determine whether a change in dietary fat was responsible for any part of the seasonal effect, but it seems unlikely that such a change, if present, was very large.

Observations on Other Variables

Although not the immediate subject of study, the data concerning the height, weight, blood pressure, heart rate, smoking habits, and parental history of the subjects have also been examined (Table 3). The findings with respect to weight are particularly pertinent, in view of the various opinions regarding its relationship to cholesterol level.[13] For the 24 subjects, there was an average weight increase of 1.7 pounds between January and October; considered individually, 15 subjects gained, one had no change, and eight subjects lost weight. This is in contrast to the fact that 23 of the 24 subjects had a fall in cholesterol level between January and October (Tables 1 and 2). The largest decreases in cholesterol level, in terms of per cent, when January and October values are compared, were observed in subjects 14 and 13, with falls of 36.2 and 32.5%, respectively. During this period subject 14 gained 3.4% body weight, and subject 13 lost 5.8% body weight, which are modest changes in opposite directions. Scatter diagrams relating cholesterol and weight changes between January and October showed no correlation, regardless of whether a percentage scale or absolute values were used. Accordingly, the large differences observed in cholesterol level between January and October cannot be explained on the basis of weight changes.

Inspection indicates little difference between the mean values for January and October in regard to height, systolic pressure, and heart rate; mean diastolic pressure was consistently lower in all three groups in October.

During this study, all the prisoners were smokers with the exceptions of subject 18, a nonsmoker, and subjects 20 and 14, who had stopped smoking a year before (Table 4). The seasonal cholesterol pattern was found among smokers, former smokers, and in the nonsmoker. Cigar and pipe smokers were in no way atypical.

We do not know whether the prisoners smoked the same amount the year around, but have no reason to believe otherwise. The smoking habits of the subjects' parents, recorded in Table 4 as a matter of interest, show a preponderance of regular smokers among the fathers and nonsmokers among the mothers.

Inquiry into parental history revealed hypertension in three fathers and six mothers; both parents of subject 21 were affected (Table 4). After developing hypertension, two fathers subsequently had heart attacks and one, a stroke; three mothers also had strokes. There was no instance of coronary disease without hypertension. The average age at onset of hypertension was 41 years in the seven parents for whom it was recorded. Three parents died of cardiovascular disease at ages 56 and 57 and one at age 38. The living fathers averaged 55 years of age, the living mothers, 49 years. There was no apparent correlation between the occurrence of parental hypertension and the prisoners' mean cholesterol level or its seasonal variation. The numbers studied are too small to permit any estimate of the relationship of parental coronary disease to these factors.

Discussion

The basic fact emerging from this investigation is that a similar seasonal trend in cholesterol level was found among the majority of the young, healthy prisoners studied, regardless of their average cholesterol levels. The high plateau reached in December and January contrasts strikingly with the low levels found in May and June. To our knowledge, the only periodic stress to which the prisoners as a group were subjected was the imponderable psychologic pressure attendant to the Christmas season. A few prisoners had an increase in outdoor physical activity with the advent of spring, but the present studies give no indication that this is the chief explanation for the marked decline in cholesterol level between March and May. Also, it seems doubtful, in view of the work of other investigators, whether the seasonal dietary changes were sufficiently great to account for a mean change in cholesterol level of the magnitude described, even if some reduction in fat intake actually occurred during the spring and summer months. In particular, studies by Hatch et al. showed that restriction of dietary fat from 85 gm. to 55 gm. (or even to 20 to 40 gm.) daily did not reduce the cholesterol levels of hypertensive patients significantly.[14]

The question of seasonal variation in serum cholesterol level has not, to our knowledge, been carefully investigated. In 1924, Currie, in Glasgow, reported that "in normal blood there is a seasonal rhythm in cholesterol concentration" and claimed that cholesterol levels were higher in summer than in winter.[15] His data on a few normal subjects were not published; most of his paper was devoted to observations taken at four times during the year on small groups of different patients with various forms of malignancy, who were heterogeneous as to age, sex, and disease status. Only one patient had determinations at all four seasons of the year. In 1932, McEachern and Gilmour, in Canada, stated that they could not confirm Currie's findings; they found no seasonal difference in cholesterol values.[16] Again, no attempt was made to observe the same subjects at different times of the year; only average cholesterol values for small groups of different

subjects were presented. Judged by modern standards of experimental design, neither of these investigations was adequate, and, as Gordon pointed out, sound conclusions cannot be drawn from them.[5]

The only recent reference to seasonal cholesterol patterns found is a report by Means and Andrews who attempted to determine, in ewes, whether a theoretical increase of thyroid activity during cold weather is accompanied by a decrease in cholesterol level.[17] They reported no significant difference in the seasonal cholesterol levels of ewes living in a naturally fluctuating seasonal environment. Their data, however, show that the highest mean cholesterol level for several groups of ewes occurred on December 21, with other high levels in March, April, and October. The lowest levels for these same groups occurred in May and September. Their findings, therefore, are somewhat similar to ours.

From our limited observations there was no striking correlation between the amount of physical activity and the cholesterol level. It is also open to question whether seasonal changes in dietary fat or stress at the Christmas season played any important role. It seems quite possible that there are other biologic or technical factors more closely associated with the observed seasonal trend of cholesterol level than those so far considered. Several

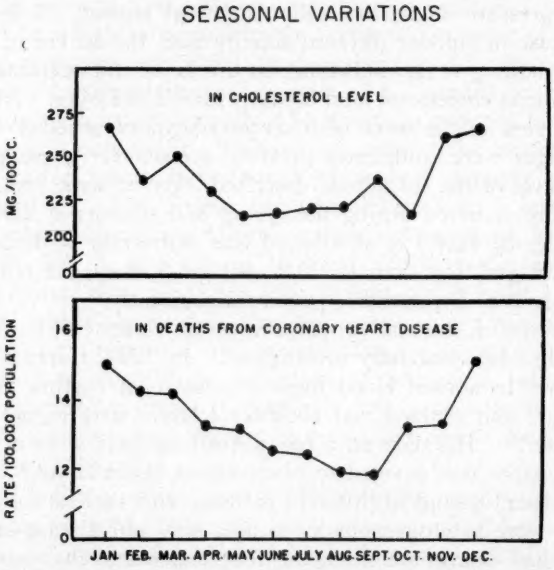

FIG. 3. Comparison of mean monthly cholesteral levels for 16 prisoners in Group A with death rates from coronary heart disease in the United States in 1958. (Vital Statistics of the United States, 1958, Vol. II, page 121, U. S. Government Printing Office, Washington, D. C., 1960.) In the cholesterol graph, the value plotted for December was actually obtained on Dec. 4, 1958, *before* the other monthly values (Table 1 and Fig. 2). It has been transposed to the other end to conform to the calendar year.

recent references have noted seasonal variations in the activity of certain endocrine glands. MacKinnon and MacKinnon found a seasonal rhythm in the morphology of the suprarenal cortex in women.[18] Osiba studied the seasonal variations in activity of the thyroid gland in healthy male Japanese students at monthly intervals for from one to two years.[19] He found the basal metabolic rate highest in December, January, and March and lowest in August. His findings are in the opposite direction to ours, since it has been established that hyperactivity of the thyroid gland in man is associated with lower cholesterol levels. There is still much to be learned concerning fundamental biologic rhythms. Without drawing any conclusions as to their possible relationship, it is worthy of note that the seasonal variation in mortality rate from coronary heart disease in the United States bears a marked resemblance to the seasonal pattern in cholesterol level revealed in the present study (Figure 3).

The concept of seasonal variations in cholesterol level adds another dimension to the complexities of cholesterol variability. The applicability of our observations to groups of subjects studied in other locations by other investigators using other chemical methods of cholesterol measurement is as yet unexplored. However, until this hypothesis is disproved, it behooves those who are making studies of cholesterol-lowering substances to design their experiments in such a way that they will not be led astray by seasonal effects, whatever they may be.

Summary

1. Monthly cholesterol determinations were made over the period of a year on 24 healthy white male prisoners aged 22 to 28 to observe the effect of the season of the year on cholesterol level.

2. Highly significant seasonal variations were found, with the highest cholesterol values occurring in the winter months and the lowest levels in the late spring, summer, and early autumn.

3. In the group of 16 prisoners on whom monthly data were complete, the mean cholesterol level lay between 260 and 265 mg. per 100 ml. during December and January and reached 260 mg. per 100 ml. again the following November.

4. In contrast, the mean cholesterol values for the same group of 16 subjects were 214.5 mg. per 100 ml. in May and 216.5 mg. per 100 ml. in June, remaining relatively low until autumn.

5. When subjects were grouped according to cholesterol level, this cyclic seasonal cholesterol pattern was found to be present in all three groups: low, intermediate, and high.

6. When the mean monthly cholesterol values for the entire group of 24 subjects are compared, two at a time, using only the eight dates when data were complete, absolute mean differences of from 43.2 to 25 mg. per 100 ml. were found which were significant at the $P < .001$ level.

7. The highly significant decrease in mean cholesterol level between January and October for the 24 subjects was not paralleled by any loss of body weight for the group, when weight data for the same two months are compared.

8. The possible seasonal influence of three factors on cholesterol level is discussed: (a) A theoretical possibility exists that emotional stress associated with the Christmas season contributes to the elevated winter cholesterol level; if so, it operates over a period of many weeks; (b) While there was some increase in physical activity among the prisoners during the months when cholesterol levels were low, there was no clear-cut evidence that this was of major importance in accounting for the observed seasonal variations; (c) Because records of monthly purchases of major items of dietary fat and analysis of randomly selected menus gave conflicting information as to the existence of a definite reduction in the fat content of the prison diet during the period of low cholesterol levels, and because we have no direct information concerning the individual consumption of fat, it is uncertain whether or not the seasonal cholesterol variation can be attributed solely to changes in dietary fat.

9. It therefore appears either that the seasonal trends observed are largely the resultant of small differences in the same direction brought about by changing patterns of stress, physical activity, and diet combined; or that some other factor or factors, either biologic or technical, not considered in this study, are largely responsible for the seasonal variation in cholesterol level.

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We should like to express our appreciation to Mr. James W. Curran, Superintendent of Prisons; Mr. Vernon L. Pepersack, Warden; and the Board of Correction for their kind permission to carry out these studies and to other members of the Maryland State Penitentiary staff for their cooperation and assistance.

SUMMARIO IN INTERLINGUA

Determinationes mensual del cholesterol esseva facite durante un anno in 24 medicalmente normal mascule prisioneros de racia blanc de 22 a 28 annos de etate pro observar le effecto del saisones del anno super le nivello de cholesterol. Esseva trovate variationes saisonal de alte signification statistic, con le occurrentia del plus alte valores durante le menses de hiberno e del plus basse nivellos in le primavera avantiate, le estate, e le prime parte del autumno.

In le gruppo de 16 prisioneros in qui le registration del datos esseva complete, le nivello medie de cholesterol esseva inter 260 e 265 mg per 100 cm³ durante decembre e januario e re-attingeva 260 mg per 100 cm³ le sequente novembre. Per contrasto con isto, le valores medie pro cholesterol in iste mesme gruppo de 16 subjectos esseva 214,5 mg per 100 cm³ in maio e 216,5 mg per 100 cm³ in junio. Illos remaneva relativemente basse usque le autumno.

Quando le subjectos esseva dividite in tres gruppos secundo le grado de concentration de cholesterol, i.e. basse, intermediari, e alte, le mentionate cyclicitate saisonal del valores pro cholesterol esseva retrovate in cata un. Quando le valores mensual medie de cholesterol pro le complete gruppo de 24 subjectos es comparate

in pares de duo e con restriction al octo datas pro le quales le registrationes esseva complete, absolute differentias medie de inter 43,2 e 25 mg per 100 cm^3 es trovate. Isto es statisticamente significative al nivello de P infra 0,001.

Le altemente significative reduction del nivello medie de cholesterol inter januario e octobre in le 24 subjectos non esseva accompaniate in parallela per ulle perdita de peso corporee in le gruppo total quando le datas pro le mesme duo menses esseva comparate.

Es discutite le possibilitate de un influentia saisonal de tres differente factores super le nivello de cholesterol. (1) Il existe un possibilitate theoric que le stress emotional que se associa con le saison de noel contribue al elevation del nivellos hibernal de cholesterol. Si isto es correcte, il se tracta de un effecto que es presente durante un periodo de multe septimanas. (2) Durante que il occurreva un certe augmento del activitate physic del prisioneros durante le menses quando le nivellos de cholesterol esseva basse, nihil indicava con nette evidentia que isto esseva de signification major in explicar le observate variationes saisonal. (3) Viste que le documentation pro le acquisition mensual del major lotes de grassia dietari se trovava in conflicto con le analyse de aleatorimente seligite specimens de repasto con respecto al possibile occurrentia de un definite reduction del contento de grassia in le dieta al prision durante le periodo del basse nivellos de cholesterol e viste, in plus, que nos ha nulle information concernente le consumption individual de grassia, il es incerte si o non le variation saisonal de cholesterol pote esser explicate exclusivemente per alterationes in le quantitates de grassia dietari.

Per consequente il pare (1) que le observate tendentia saisonal es in grande mesura le producto de micre differentias del mesme orientation que resulta de un combination de alterationes in le modos de stress, die activitate physic, e de dieta o (2) que un altere factor o altere factores de character biologic o technic e non prendite in consideration in le presente studio es primarimente responsabile pro le variationes saisonal del nivellos de cholesterol.

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AORTIC SURGERY IN MARFAN'S SYNDROME. HEMODYNAMIC AND HISTOLOGIC RESPONSE *

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ANEURYSMAL dilatation of the ascending aorta and aortic sinuses with cystic degeneration in the media are well recognized manifestations of Marfan's syndrome.[1] The relentless progression of the aortic insufficiency which accompanies and, indeed, aggravates the medial change, and the frequent occurrence of acute aortic dissection have stimulated several surgical attempts at correction. Insertion of a prosthetic (Hufnagel) valve, ligation of the aortic annulus, partial excision of the aneurysm, and wrapping of the aorta with plastic, have been reported.[1-3] Despite these surgical attempts, there has been little histologic information about the response of the aorta burdened with medial cystic necrosis to surgical intervention.

We are reporting a case of severe aortic regurgitation and aneurysmal dilatation of the ascending aorta, in whom a clinical diagnosis of Marfan's syndrome was established on the basis of abnormalities in the children. An artificial aortic valve was inserted in an attempt to relieve advanced heart failure, but the patient died three months later from a tear in the aorta at the site of valve insertion. Dye dilution studies and estimations of cardiac output and regurgitant flow before and after operation were performed. At autopsy an aneurysm of the abdominal aorta was discovered.

CASE REPORT

E. P., a 39-year-old embalmer, was admitted to The New York Hospital for the first time on December 4, 1957, complaining of progressive dyspnea on exertion. Four years earlier an enlarged heart had been detected. Bilateral long-standing inguinal hernias were repaired in 1955. Nine months prior to admission he had developed dyspnea, orthopnea, ankle edema, and frequent drenching sweats.

During the next eight months the patient progressively deteriorated. Nocturnal dyspnea, cough, and orthopnea persisted. He experienced severe dyspnea after walking a short distance and especially following sexual intercourse. Finally, he became unable to work, and was referred to The New York Hospital for possible corrective surgery.

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There was no history of rheumatic fever or venereal disease. There was no family history of heart disease or arthritis. His father died at the age of 39 of "pneumonia." Three younger brothers were living and well. Physical examination revealed a large white male (Figure 1) in moderate respiratory distress. His blood pressure (right arm, supine) was 195/50 mm. Hg; pulse 88 and regular; respirations, 20/min.; temperature, 37.8° C. by rectum. He weighed 100 Kg. and was 188 cm. tall. His extremities and digits were unremarkable, save for bilateral fifth hammer toes. Complete ophthalmologic examination revealed that the eyes were normal except for mild myopia. The neck veins pulsated normally. The chest was normal. The lungs were clear to percussion and auscultation. A tender liver extended two fingerbreadths below the costal margin. There was moderate pretibial edema.

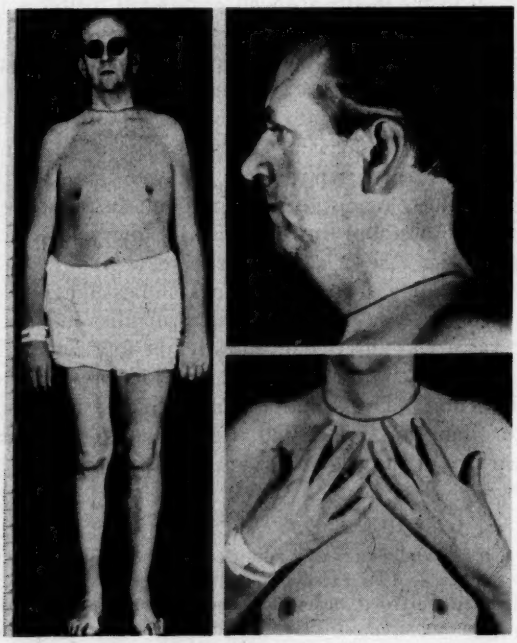


FIG. 1. Patient E. P., aged 39, with free aortic insufficiency due to Marfan's syndrome. Note dolichocephaly, bilateral hammer toes.

The heart was greatly enlarged with a diffuse heaving apical impulse in the sixth intercostal space at the midaxillary line. The first sound at the apex was muffled. The second sound was accentuated. A very loud diastolic decrescendo murmur accompanied by a fine purring thrill radiated from the aortic area down the *right* sternal border and could be heard at the apex. A coarse systolic murmur and thrill radiated from the aortic area into the neck. There was a short, early diastolic rumble at the cardiac apex. Duroziez' sign and Quincke and Corrigan pulses were readily demonstrated.

A complete blood count and urinalysis were normal. A serologic test for syphilis (Mazzini) was negative. An electrocardiogram revealed left axis deviation, PR interval 0.21 seconds, QRS duration 0.13 seconds. The tall R_1, $V_{5,6}$ and deep S_3, V_1

with RT-segment depression and T-wave inversion in leads 3, V_5, V_6, were compatible with left ventricular hypertrophy.

Angiocardiograms: Angiocardiograms performed prior to surgery revealed a greatly enlarged heart (Figure 2). The left ventricle was huge; the left atrium was moderately enlarged. A large aneurysm of the ascending aorta displaced and indented the superior vena cava and the enlarged right atrium and right ventricle. Dilatation of the aorta was maximal just above the aortic sinuses. Proximal to the innominate artery the aorta abruptly tapered to normal caliber. The aneurysm measured 12 cm. in diameter at its greatest width and, assuming a spherical shape, was calculated to contain more than 700 ml. of blood. There was no evidence of aortic dissection.

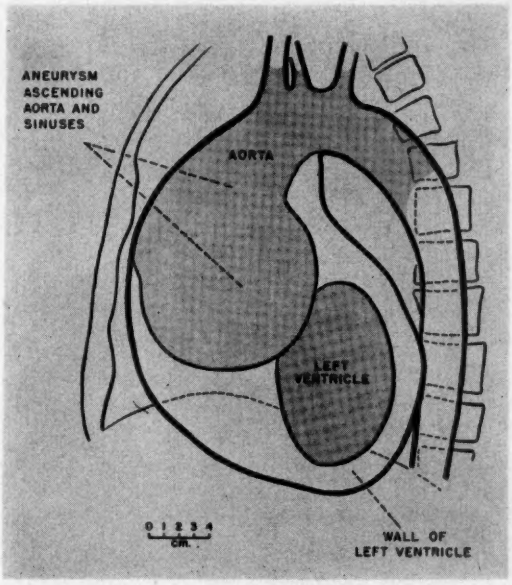


FIG. 2. Direct tracing of preoperative angiocardiogram, left lateral view. Note huge aneurysm of sinuses of Valsalva and ascending aorta, greatly enlarged left ventricle.

On January 6, 1958, the patient developed a painful mass in the right groin, 5 cm. in diameter. Operation disclosed an incarcerated femoral hernia strangulating a loop of small bowel, which was repaired without difficulty. Recovery from this procedure was uneventful.

On January 24, 1958, a Hufnagel prosthetic valve was inserted in the descending aorta distal to the left subclavian artery. The aorta at the operative site was of normal diameter, but sections from a small segment revealed medial elastic degeneration. On the seventh postoperative day the patient developed severe "tearing" pain substernally and in the left chest, which required narcotics for relief. Five days later a roentgenogram of the chest revealed for the first time a hazy density encircling the arch of the aorta at the site of the prosthetic valve (Figure 3).

He had no further chest pain and was discharged on the thirty-second postoperative day. For the next two months his exercise capacity and respiratory

symptoms were little changed from those recorded preoperatively. The radiographic shadow around the aortic arch was unchanged.

On April 21, 1958, he was readmitted with crampy abdominal pain, diarrhea, and knifing pain in the left calf. His blood pressure was 190/? (right arm, supine), pulse 100 and regular, respiration rapid and shallow, and temperature 38.9° C. Examination of the lungs, chest, and heart was unchanged. Bowel sounds were active. A pulsatile fusiform mass was palpated in the abdominal midline. The left calf was cool and the left dorsalis pedis could not be palpated. During the next week the patient had evidence of repeated emboli to the bowel, spleen, and lower extremities. One week after admission he developed severe, sharp retrosternal pain similar to the

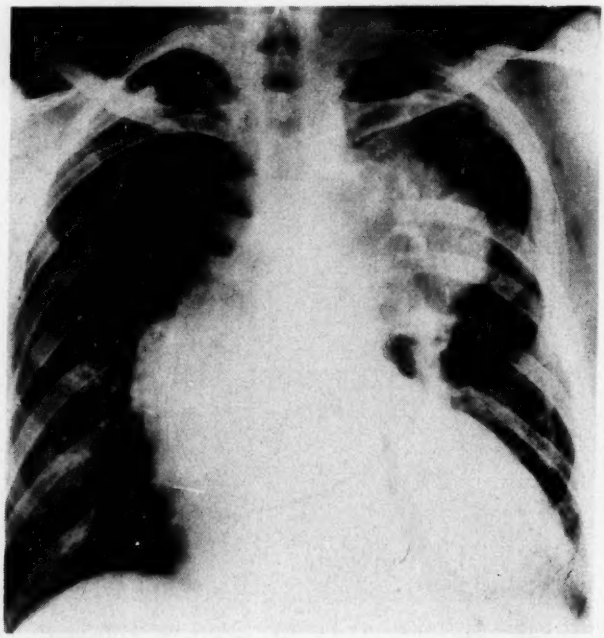


FIG. 3. Postoperative chest film. Shadow of "false" aneurysm surrounds site of Hufnagel valve insertion below aortic knob. Upper right cardiac border is formed by aneurysm of ascending aorta.

pain which had occurred postoperatively. Shortly thereafter he suffered repeated massive hemoptyses, his blood pressure slowly declined, and he died May 1, 1958.

Family History: Specific questioning revealed suggestive evidence of Marfan's syndrome in the family. It was stated that the patient's three brothers were tall and wore glasses, but they were not available for examination. One had recently been discharged from the Marines. Several members of the patient's wife's family were also described as tall and thin. All three of the patient's children were of excessive height and myopic, and one was said, in response to a direct question, to have dislocated lenses. The children were promptly examined, and stigmata of Marfan's syndrome were evident in all three (Figure 4).

E. P., aged 12, was 176.5 cm. tall (normal for age 147 ± 7.5 cm.) and weighed

59.7 Kg. His head was dolichocephalic with a high arched palate. Limbs and digits were long and thin. He had severe myopia. The lenses were in normal position. He had a moderate pectus carinatum. There were no cardiac murmurs. Cardiac fluoroscopy and chest roentgenograms were normal, as was an electrocardiogram.

R. P., the identical twin of E. P., was 176.5 cm. tall and weighed 57.5 Kg. The physical and laboratory findings were identical with those of the twin.

T. P., aged seven, was 145 cm. tall (normal for age 122.5 ± 5 cm.) and weighed 31 Kg. He had dolichocephaly, high palate, dolichostenomelia, and arachnodactyly. In addition bilateral subluxation of both lenses and high grade myopia were present. There was a moderate pectus-type of chest deformity. No cardiac murmurs were

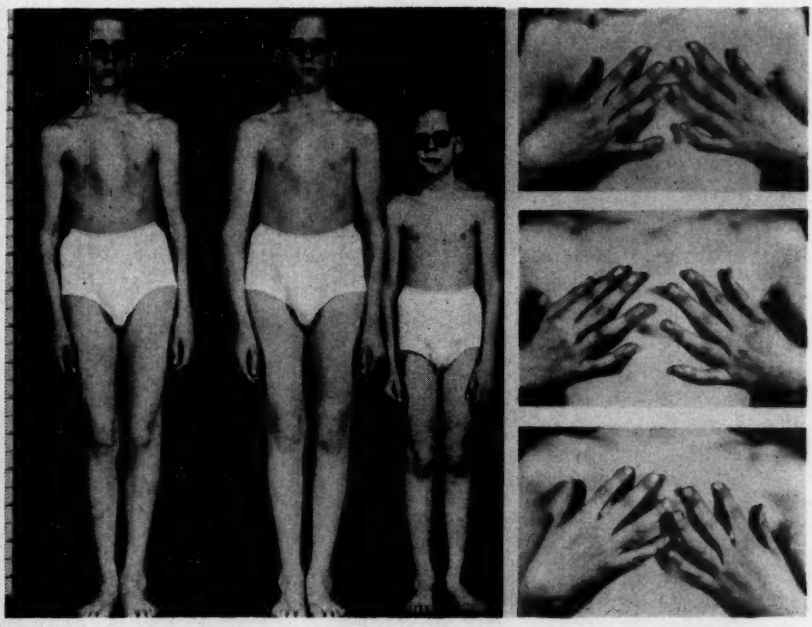


FIG. 4. Children of E. P. with Marfan's syndrome. Twins, aged 12, have dolichocephaly, high myopia, pectus carinatum, arachnodactyly. Youngest, aged 7, has bilateral lenticular subluxation, slight pectus excavatum. None has heart disease.

heard. An electrocardiogram was normal. Chest roentgenogram revealed evidence of an anomalous left subclavian artery; the aorta appeared normal.

Hemodynamic Studies: Hemodynamic data were obtained before and six weeks after insertion of the prosthetic valve (Table 1). Dye dilution curves were recorded with a Waters oximeter earpiece utilizing an Electronics for Medicine preamplifier and a Sanborn "Polyviso" recorder, following the rapid injection of a known amount of T-1824 into a peripheral vein from a special syringe adaptor. Cardiac output, "central" blood volume, and the reciprocal of the slope of the descending limb of the redrawn dye dilution curve (1/s) were calculated according to standard methods.[4] Postoperatively the arterial pulse pressure proximal to the valve was considerably wider than that preoperatively recorded from the femoral artery, although the mean pressures were similar. The femoral artery pressure recorded postoperatively dif-

fered in several respects from that of the brachial: pulse pressure was narrower with a lower systolic and higher diastolic pressure, and mean pressure was higher. In addition, the femoral arterial pressure pulse showed distinct evidence of a dicrotic notch and wave, which had not been present previously.

The cardiac index was unchanged following operation and the pre- and post-operative "central" blood volume did not differ significantly. Some assessment of the rate of regurgitant flow may be attempted by comparing the reciprocals of the slope (1/s) derived from the two studies. Experiments in models indicate that under certain conditions the volume of regurgitation influences the downslope of a dye dilution curve, and that the ratio 1/s provides an index of the rate of regurgitation.[5, 6] The validity of this relationship in man remains to be demonstrated. Since 1/s, the cardiac output, and the "central" blood volume are similar in both studies, the data may be interpreted to indicate little change in the regurgitant flow across the aortic valve following the operative procedure.

Autopsy Findings: Significant post-mortem findings were limited to the cardiovascular system. The heart weighed 900 gm. The left ventricle was massive, being

TABLE 1

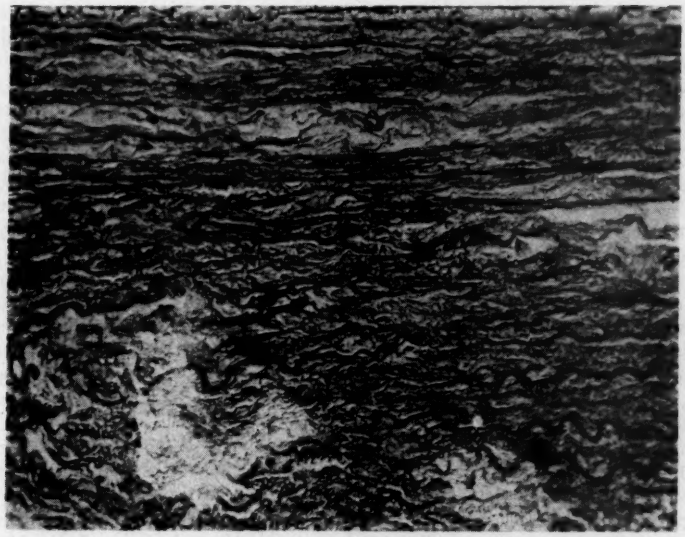
Hemodynamic Data

	Before Operation	One Month After Operation
Body surface area, sq. M.	2.22	2.08
Heart rate, beats/min.	85	85
Arterial pressures, mm.Hg Systolic/diastolic, mean		
Brachial pressure	—	201/30
Mean pressure		77
Femoral pressure	164/72	152/86
Mean pressure	78	109
Cardiac output, L./min.	7.00	6.59
Cardiac index, L./min./M²BSA	3.15	3.16
"Central" blood volume, L.	4.97	4.12
1/s	17 8	19.5

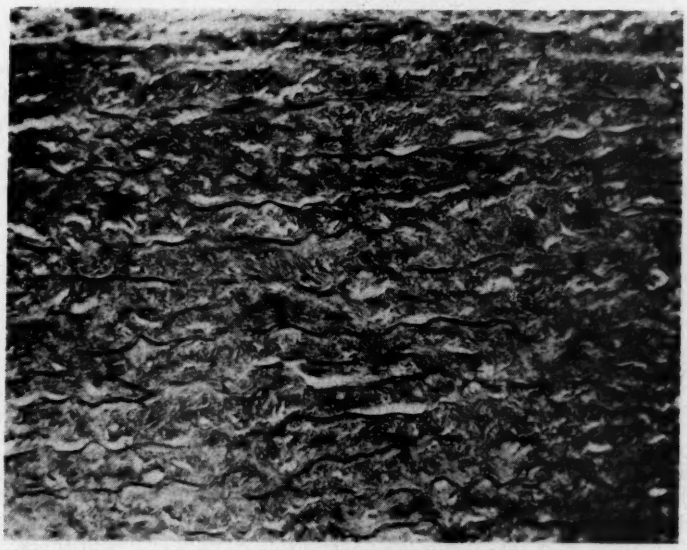
both dilated and hypertrophied, and its wall measured 20 mm. in thickness. The aortic valve was 105 cm. in circumference, and was insufficient. The aortic leaflets were stretched and redundant but did not adequately close the greatly enlarged orifice. The left atrium was moderately dilated. The mitral, tricuspid, and pulmonic valves were normal.

The ascending aorta was deformed by a huge saccular aneurysm. A smaller fusiform aneurysm of the abdominal aorta extended from the renal arteries to the bifurcation. The saccular aneurysm included the sinuses of Valsalva and had a maximal circumference of 28.5 cm. some 8 cm. above the aortic valve. The coronary orifices were displaced superiorly in the greatly dilated aortic sinuses. Proximal to the innominate artery the aorta abruptly narrowed to a normal circumference of 6.3 cm. and was normal in caliber to the renal arteries. The fusiform aneurysm was 7.5 cm. in its greatest circumference, swelling distal to the renal and tapering proximal to the iliac vessels.

Distal to the left subclavian artery at the superior point of attachment of the aorta to the plastic valve there was a 5 mm. tear through the aortic wall. It was surrounded by a huge organized blood clot. A blood-filled fistulous tract could be



A



B

FIG. 5. Response of adult aorta to plastic valve insertion. Hematoxylin and eosin × 100. A. Rheumatic heart disease 14 months after insertion of Hufnagel valve, 2 cm. from prosthesis. Note loss of smooth muscle nuclei. B. (E. P.) Marfan's syndrome, three months after operation, 2 cm. proximal to valve. Note extensive cystic degeneration of elastic fibers combined with paucity of smooth muscle nuclei.

traced from the tear into the left main bronchus. A thrombus partially occluded the superior portion of the artificial valve. There were multiple small recent infarcts in the spleen and in both kidneys.

Sections of the dilated ascending aorta revealed striking changes. The elastic lamellae of the media were fragmented and widely separated by material stained blue with the periodic acid-Schiff alcian blue stain. In some areas the elastic lamellae appeared to be condensed and flattened by the accumulation of mucoid material. Accompanying the irregular arrangement of the elastic lamellae was an associated clustering of smooth muscle fibers and collagen. There were multiple large dilated nutrient arteries in the adventitia and in the media.

Multiple sections from the aorta at all levels revealed a definite pattern to the medial abnormality: the degree of elastic change corresponded with the degree of aortic dilatation. Sections taken from the ascending thoracic and the abdominal aneurysmal areas of maximal dilatation revealed the most marked medial degeneration. As the dilated aorta tapered to normal caliber proximal to the innominate artery and at either end of the fusiform aneurysm the elastic changes became progressively less intense. Except for patchy areas of medial change distal to the ligamentum arteriosum and near the celiac axis, the remainder of the aorta was normal.

The smooth muscle of the media was not involved by the degenerative process involving the elastica. However in the immediate region of the Hufnagel valve for a distance of 1 to 2 cm. proximal and distal to the valve's attachment to the aorta by the encircling and compressing multiple-fixation-point ring, the smooth muscle was replaced by fibrous scar tissue. Few nuclei remained. An organized thrombus was firmly attached to the intima over this region of "devitalized" media proximal to the valve. Both smooth muscle necrosis and elastic degeneration coincided in the region of the tear proximal to the valve (Figure 5). The segment below the valve showed only smooth muscle changes.

To determine the response of the non-Marfan's aorta to incision and insertion of a Hufnagel valve, the autopsy specimens from three patients with rheumatic heart disease who died two weeks, 14 months, and 18 months after operation were examined. In a short segment above and below the valve all three had necrosis of the smooth muscle in the media with replacement by fibrous tissue (Figure 5). In contrast to the patient with Marfan's syndrome, none had changes in the elastica.

Discussion

Although Marfan's syndrome is not a common cause of aortic insufficiency, the implications of such a diagnosis emphasize the importance of close scrutiny of all patients with isolated aortic insufficiency. The clinical diagnosis of Marfan's syndrome in this patient was made from the combination of aortic regurgitation in him and the characteristic skeletal and ocular abnormalities in his children. The diagnosis was corroborated by the angiocardiogram,[7] the aortic biopsy, and post-mortem findings. Radiation of the diastolic aortic murmur and thrill down the chest along the right sternal border was an impressive finding on repeated examination. This unusual sign is probably a reflection of extreme dilatation and displacement of the ascending aorta toward the right chest.

Hufnagel procedures have been reported in four patients with Marfan's syndrome.[1-3] Three died postoperatively, one from an aortic tear at the site of valve insertion, one from aortic dissection, and one from intractable heart

failure. One patient survived and did well. Insertion of a Hufnagel valve was undertaken in the patient reported above in an attempt to relieve intractable left ventricular failure; there was little symptomatic improvement. Cardiac output at rest was unchanged postoperatively, and the dye dilution data indicate that the regurgitant flow was probably the same as preoperatively. Although it has been stated that a Hufnagel valve may reduce the aortic regurgitation by as much as 75%,[8] few measurements in man have been recorded. The aneurysm of the ascending aorta was estimated to contain almost a quart of blood, a reservoir ever ready to flow back into the left ventricle during diastole and uninfluenced by a prosthesis at the level of the left subclavian artery. Successful reduction of aortic regugitation when the ascending aorta is greatly dilated will depend upon surgical manipulation in the region of the valvular ring.

A fusiform abdominal aneurysm was palpated just before the patient died. This finding was confirmed at autopsy. It was not recognized prior to the operation and may have developed after the procedure. Abdominal aneurysms are uncommon in Marfan's syndrome, although several have been reported to date.[1] In one case evidence of medial degeneration was confined to the aneurysm; the ascending aorta was normal grossly and microscopically.[9] Moderate dilatation of the descending thoracic aorta is not uncommon in Marfan's syndrome and may be related to slight narrowing of the aortic lumen at the isthmus.

Direct femoral arterial pressure pulses from patient E. P. prior to the operation demonstrated the characteristic pulse curve of severe aortic insufficiency with a complete lack of incisura or evidence for a standing wave.[10] Postoperatively the femoral pulse pressure not only was lower than the brachial, but in contrast to the brachial tracing the femoral tracing showed a clear-cut anacrotic notch and dicrotic wave suggesting that the Hufnagel valve provided adequate closure of the proximal aorta at end-systole and initiated a standing wave in the lower aorta.[11] Possibly the change in hydrodynamic forces in the lower aorta following insertion of the valve influenced the development of the abdominal aneurysms.

In this patient with Marfan's syndrome the smooth muscle necrosis at the operative site was inadequately buttressed by the other elements of the media and a horizontal tear occurred in the aorta across the edge of the valve, a region where the aorta was whipping back and forth against the relatively fixed plastic edge with each heart beat. The location and gross appearance of the tear suggested a crack such as occurs with wear in stethoscope tubing at its junction with the metallic headpiece. The small tear where both elastica and smooth muscle were deficient probably occurred one week after operation when the patient experienced severe chest pain and developed a "false" aneurysm. Dimond et al.[3] reported a patient with Marfan's syndrome whose aorta tore at the site of a Hufnagel valve, but they did not give histologic details. The first few days after aortic surgery,

before a firm aortic scar replaces the damaged smooth muscle, are probably the most crucial.

Cystic medial necrosis or Erdheim's lesion, although characteristic of Marfan's syndrome involving the vascular system, is not specific. It has been observed in the dilated ascending aortas of aortic stenosis;[12-17] aortic insufficiency;[17-18] bicuspid aortic valve with aortic insufficiency;[19-20] coarctation;[21-22] in the poststenotic dilatation distal to a coarctation;[17] in the dilated pulmonary artery of patent ductus arteriosus;[23] and in experimental pulmonary artery stenosis.[24] It is noteworthy that one of Gsell's[13] and both of Erdheim's original cases had aortic valvular disease, one of the latter[12] having "hochgradige" stenosis with an acute aortic dissection beginning in the poststenotic dilatation.

The occurrence of Erdheim's lesion in the dilated aorta or pulmonary artery of a wide variety of lesions producing excessive pulse pressures or jet-flow suggests that kinetic forces play an important role in pathogenesis. Further indication of a relation between intravascular forces and Erdheim's lesion is the frequent clinical or pathologic evidence suggesting abnormal hemodynamics in the lesser circulation in Marfan's syndrome when the pulmonary artery is involved.[25-27]

If, as seems reasonable, the microscopic findings at the operative site in patient E. P. can be applied in general, incision and repair of the aorta in patients with Marfan's syndrome may be hazardous. Loss of smooth muscle along the suture line may be poorly tolerated when the elastica is already defective. Direct attempts to reduce aortic insufficiency or to replace dissecting aneurysms with grafts may be limited by postoperative aortic breakthrough along the incision. Further studies of patients with Marfan's syndrome subjected to vascular surgery will be necessary before a definite conclusion can be formed.[28]

Many of the cardiac abnormalities not associated with Marfan's syndrome in which Erdheim's lesion has been demonstrated are potentially surgically correctable. Incision through an artery in an area of elastic degeneration may also have disastrous consequences in these patients. As smooth muscle around the incision is replaced by scar tissue secondary to disruption of the vasa vasorum, the elastic fibers may be inadequate to prevent tear or rupture. Since Erdheim's lesion is generally most extensive where these vessels have been stretched, it would probably be wise to avoid an operative approach through a dilated segment of aorta or pulmonary artery.

Summary

A patient with Marfan's syndrome, aneurysmal dilatation of the ascending aorta, and severe aortic regurgitation had an artificial (Hufnagel) valve inserted in the descending thoracic aorta. Cardiac output and the reciprocal of the downslope of dye dilution curves were similar before and after

operation. The patient died three months after operation from a tear in the aorta at the site of the prosthetic valve. At autopsy an aneurysm of the abdominal aorta was demonstrated in addition to the aneurysm of the ascending aorta.

Degeneration of the elastica was present in the aortic media of both aneurysms. The severity of the elastic degeneration correlated well with the degree of aortic widening. The fatal aortic tear occurred superior to the prosthesis where smooth muscle necrosis of the media secondary to the operative procedure was combined with pre-existing elastic change.

It is concluded that the aorta of Marfan's syndrome tolerates incision poorly in regions of elastic medial degeneration. Since medial elastic degeneration occurs in dilated vessels of a wide variety of cardiac disorders, the histologic observations reported herein may have general significance.

Acknowledgments

The hemodynamic studies were performed by Drs. A. Lee Winston, Lucien I. Arditi, and Daniel S. Lukas. Dr. Lukas contributed helpful suggestions during the preparation of the manuscript.

The observations reported herein would not have been possible without the willing cooperation of the patient and his family.

Summario in Interlingua

In un patiente con syndrome de Marfan e con dilatation aneurysmal del aorta ascendente e sever regurgitation aortic, un valvula artificial (Hufnagel) esseva inserite in le descendente aorta thoracic. Le rendimento cardiac e le reciproco del coefficiente de declino in le curvas de dilution de colorante esseva simile ante e post le operation. Le patiente moriva tres menses post le operation in consequentia de un ruptura in le aorta al sito del valvula prosthetic. Le necropsia revelava un aneurysmo del aorta abdominal, a parte le aneurysmo del aorta ascendente.

Degeneration del elastica esseva presente in le media aortic de ambe aneurysmos. Le severitate del degeneration elastic esseva ben correlationate con le grado del allargamento aortic. Le mortal ruptura aortic occurreva in supra del prosthese ubi necrose de musculo lisie del media secundari al intervention operatori esseva combinate con pre-existente defectos del elastica.

Es concludite que le aorta in syndrome de Marfan possede un basse toleration pro incisiones in regiones de degeneration elastico-medial. Viste que degeneration del media elastic occurre in vasos dilatate de un extense varietate de disordines cardiac, le observationes histologic hic reportate es possibilemente de signification general.

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PSEUDO-PSEUDOHYPOPARATHYROIDISM: REPORT OF THREE CASES IN ONE FAMILY *

By NATHANIEL UHR, M.D., F.A.C.P., and HARVEY B. BEZAHLER, M.D., *Topeka, Kansas*

IN 1942 Albright, Burnett, Smith, and Parson [1] originated the term pseudohypoparathyroidism (PH) to describe a group of patients with round face, short stature, short metacarpals and metatarsals, ectopic ossifications, elevated serum phosphorus and low serum calcium values. What differentiated these patients from persons with idiopathic hypoparathyroidism was their failure to respond with a phosphate diuresis to parenteral administration of parathyroid extract.

Ten years later the designation pseudo-pseudohypoparathyroidism (PPH) was employed by Albright, Forbes, and Henneman [2] in describing a 29-year-old woman who had many of the clinical features of PH but in whom the values for serum phosphorus and calcium were normal. In a recent paper describing eight new cases of this disorder, Hortling et al.[3] reviewed 15 others previously published; reports of eight additional cases have appeared in the past two years.[4-8, 19] Although a faulty genetic factor in the causation of the condition was recognized from the beginning, little mention was made of the possible hereditary aspects of PPH until later, when reports appeared which contained descriptions of the syndrome in more than one member of a family.

We had the opportunity recently of studying two patients, a mother and son, with this rare dyschondroplasia. A third member of the family, a younger son, is included in this report although he was not available to us for examination. From the history and the description given us by the mother, the evidence seems to us more than presumptive that he suffered with the same affliction.

CASE REPORTS

Case 1. A 20-year-old white man was admitted to The C. F. Menninger Memorial Hospital on February 18, 1959, because of a personality disorder characterized by episodic outbursts of infantile behavior and stuttering since the age of four. There were no physical complaints.

Other than the common contagious diseases, a tonsillectomy, and a circumcision, the patient had had no serious illnesses or operations. At the age of four, bony outgrowths were noted on the arms; later the rib cage and legs were involved. An orthopedic consultant advised against operation or other treatment since the condition did not interfere with his growth or activities. He found the right leg to be slightly shorter than the left. There was a history of about 10 syncopal attacks

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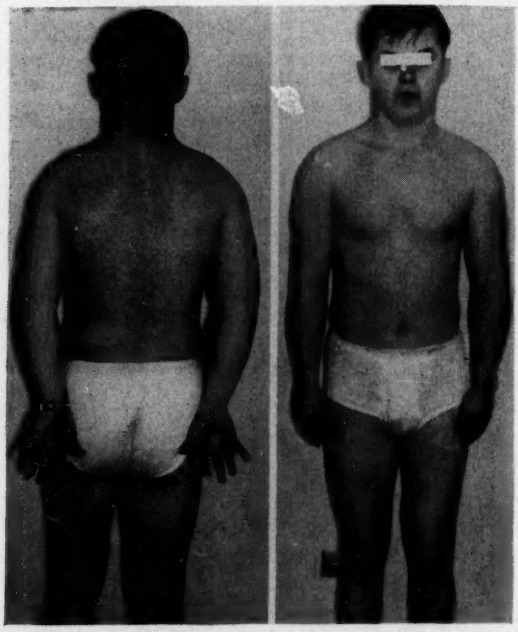

FIG. 1. *Case 1.* Note round face, short extremities, small, thick-set hands.

during his grade school years. Because of two grand mal seizures which occurred in his senior year in high school, the patient was admitted to another hospital for diagnostic studies in June, 1957. No abnormal findings were reported on clinical and neurologic examinations. Studies of the urine and blood, including estimations of the serum calcium and phosphorus, gave normal results. An electrocardiogram and two electroencephalograms were normal. Skeletal x-rays disclosed multiple exostoses. It was felt by the physicians at this hospital that the syncopal and convulsive attacks were not due to epilepsy. He was given no medication and has had no seizures since.

TABLE 1

Values for Serum Calcium and Phosphorus

Case 1			Case 2		
Date	Calcium (mg./100 ml.)	Phosphorus (mg./100 ml.)	Date	Calcium (mg./100 ml.)	Phosphorus (mg./100 ml.)
6/25/57	11.5	4.2	2/27/59	9.8	4.6
6/27/57	9.15	3.9	6/ 5/59	10.8	3.6
3/ 9/56	6.1	3.6			
3/13/59	7.8	3.4			
3/16/59	8.6	3.3			
4/ 7/59	10.2	3.9			
5/28/59	10.1	4.0			

Physical examination by us revealed an apparently healthy young man of good muscular development, 5′ 8″ tall, weighing 150 pounds. His physical appearance was striking. He had a round boyish face and disproportionately short arms and legs (Figure 1). The total arm spread was only 60 inches. The length of the right leg (measured from anterior superior iliac spine to heel) was 36½ inches, the left 37 inches. The hands were small and pudgy and the fingers stubby. The feet were everted with moderate hallux valgus; the third, fourth, and fifth toes on each foot were markedly short. Many hard bony masses of varying size and shape were palpable on the extremities. The clenched fists showed no dimpling at the usual

FIG. 2. *Case 1.* Roentgenogram of lower femur and upper tibia showing exostoses and osteochondromas.

knuckle sites (negative Albright's sign [2]). The physical and neurologic examinations disclosed no other abnormalities. Psychologic tests revealed an above-normal intelligence.

The blood hemoglobin, hematocrit, total and differential leukocyte counts, and urine examinations, including two 24-hour Sulkowitch's tests, were normal. Two electroencephalograms, one a sleep tracing, showed no abnormalities. The serum calcium and phosphorus determinations are shown in Table 1. The serum proteins, protein-bound iodine, alkaline phosphatase, urea nitrogen, and sugar were normal. The Kline test was nonreactive. An Ellsworth-Howard test [9] was not performed.

Skeletal X-rays: There was generalized minimal osteoporosis. The metaphysial portions of the shafts of the long bones showed widening instead of the normal tapered contour; they exhibited multiple exostoses and osteochondromas (Figure 2). There was brachydactylia with shortening of all of the metacarpal bones; this was most pronounced in the fourth metacarpal bilaterally. The third, fourth, and fifth metatarsals on each foot were markedly short. The distal thirds of both ulnae were hypoplastic, suggesting almost complete absence of the heads of these bones (Figure 3). The pelvis, scapulae, and ribs showed coarse trabeculation and scattered enchondromas.

Case 2. The mother of case 1 was a 43-year-old woman who considered herself frail and tired but who had never been seriously ill. In the past she had suffered occasionally with low backache and recurrent low abdominal pain which had been diagnosed as a spastic colon. At the age of 26 an abdominal operation for uterine

FIG. 3. *Case 1.* Roentgenogram of hands and distal forearms. Note shortness of metacarpals and hypoplasia of distal ulnae.

fixation and tubal ligation was performed. She had stuttered since childhood but the affliction was under better control than that shown by her son. She had two sons, 20 and 17 years of age.

On physical examination, facies and body build were similar to those of her son. The face was round and young in appearance. She was 5′ 2″ tall and weighed 100 pounds. The arms and legs were disproportionately short in relation to the torso. The arm span was 54 inches. The legs (from anterior superior iliac spine to heel) measured 33 inches. The hands and feet were small, and on clenching the fists no dimpling was observed at the normal sites of the knuckles. The physical examination was otherwise negative. The patient appeared to be of low-normal intelligence. The values for serum calcium and phosphorus are shown in Table 1.

On x-ray studies, the shafts of the long bones showed slight widening. Multiple exostoses and osteochondromas of the long bones, pelvis, and scapulae were noted. The fourth and fifth metacarpals of both hands were disproportionately shorter than the first, second, and third (Figure 4).

FIG. 4. *Case 2.* Roentgenogram of hands showing shortened fourth and fifth metacarpals.

Case 3. The patient was the younger son of case 2. He was 17 years old and said to be in excellent health. (Unfortunately this patient was not available to us for examination since the family lived a great distance from Topeka. We feel, nevertheless, that the information we have about him warrants his inclusion in this report.) He, too, had stuttered since early boyhood but the speech disorder was mild. He was said to be a well-adjusted youngster who had done well at school. The mother stated that he was built exactly like his older brother although he was a few inches shorter. She described him as having a round face, disproportionately short arms

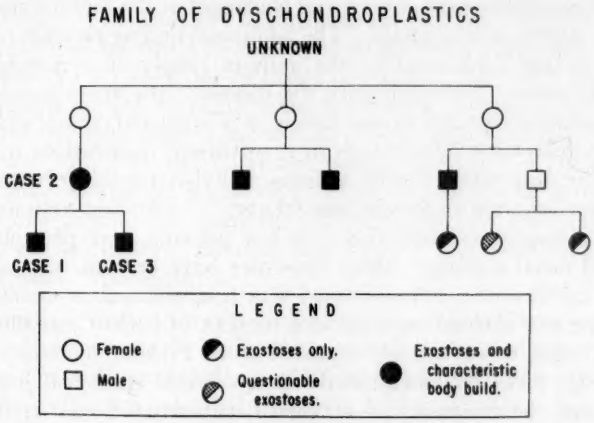

FIG. 5. Family pedigree (only cases 1 and 2 were examined).

and legs, and broad, pudgy hands. He was known to have many exostoses, one of which had to be removed from his leg because of pressure symptoms.

Additional family history was obtained by questioning the patient in case 2. This information was supplemented and confirmed by the father of case 2 (and grandfather of case 1). He reported that six other near-relatives, all first or second cousins, had some form of skeletal disorder. Of these, three had the characteristic short stature, short limbs, small wide hands, and round faces; all had had operations for the removal of bony excrescences. The other three were of normal height but were known to have had exostoses removed (Figure 5). There was no history of consanguinity.

Discussion

Pseudo-pseudohypoparathyroidism (PPH) can be regarded as an entity only when considered within the context of the relatively more common syndrome of pseudohypoparathyroidism (PH); the single distinguishing feature between the two is a biochemical one. In the former, the serum calcium and phosphorus concentrations are normal; in the latter, the serum calcium is depressed, the phosphorus is elevated, and there is a lack of response to parathyroid hormone. Other findings frequently encountered in PH such as mental retardation, subcutaneous calcifications and ossifications, lenticular opacities, a history of tetany or convulsions, and electroencephalographic abnormalities have also been described in patients with PPH. Bearing in mind, then, the chemical difference, Albright conceived of the syndromes as loosely-knit complexes in which patients might demonstrate any one, two, or combination of the above physical characteristics. Indeed, Albright mentioned "abortive" cases who showed no abnormalities whatever except unresponsiveness to parathyroid extract.

A review of the cases of PPH amply reflects this theme-and-variations concept. Included in the category, for example, is the recent report of a 40-year-old, short, stocky woman with a round face, in whom the outstanding skeletal anomalies were short distal phalanges of the thumbs and the third and fourth fingers of both hands. The additional finding of dense calcification of the aorta was considered by the authors simply as a manifestation of ectopic calcification associated with the disease.[6] In another instance, one of three members reported in one family, a 57-year-old, short, stout woman of normal intelligence, showed only tiny, soft-tissue ossifications in the hands and feet; she also suffered with diabetes and rheumatoid arthritis.[8] Three patients were reported as having blue sclerae,[10, 11] a finding commonly associated with osteogenesis imperfecta. A few patients have presented normal stature and facial contour. Bony exostoses have been at least as common as ectopic calcifications. A shortened fourth metacarpal or metatarsal bone has been the sole skeletal anomaly in a number of patients, as illustrated by six of the eight cases recently reported from Finland by Hortling et al.[3] (Incidentally, these authors carried out a valuable statistical investigation. To determine the frequency of abnormal metacarpal bones in the general population, they studied the roentgenograms of the hands of 764 normal

persons between the ages of seven and 33; not a single case of brachymetacarpalia was found.)

No two of the reported cases have been alike and all have varied considerably from the prototype, Albright's original case. Furthermore, the majority of the patients have suffered from associated systemic, endocrine, or metabolic derangements of major proportions: severe hypertension (in Albright's case), gout with splenomegaly, hypothyroidism, diabetes, gonadal dysgenesis or dysfunction, and the Pickwickian syndrome.

Is PPH a distinct entity? The answer would have to be in the affirmative in Albright's case (1952) since he described the criteria; but these were never set in a rigid diagnostic mold as illustrated by the cases reported subsequently. It is perhaps because the syndrome has lacked more precise definition that one must accept the diagnosis of PPH even in those patients who demonstrate only the most tenuous clinical relationship to the original case.

Some authors have challenged the propriety of the term PPH, since there is no parathyroid dysfunction; nor is it descriptive of the main clinical manifestations of the syndrome. Van der Werff ten Bosch [12] feels that "brachymetacarpal dwarfism (without tetany)" is a more descriptive name. Fromm [13] suggests that "the term PPH should be discarded and should be replaced in each case by the respective descriptive denomination: dyschondroplasia or exostoses with metaphysial dysplasia, or congenital skeletal malformation." So eminent an authority as Snapper [14] has also expressed disagreement with the above nomenclature and favors the designation proposed by McNeely et al.[15] of "dyschondroplasia with soft tissue calcification and ossification."

The etiology of PPH is unknown. In 1952 Albright [2] postulated that the dyschondroplasia of the metacarpals and metatarsals both in PH and PPH was a genetic disorder unrelated to the other stigmata observed in these syndromes. Wallach and his co-workers in 1956 suggested that PH and PPH, as well as myositis ossificans progressiva, were the results of errors in fetal development due to injury in utero, rather than the result of gene-determined defects.[16] Since then, however, a number of reports have demonstrated the syndrome in more than one member of a family, making it appear that both PH and PPH are genetic disorders. The possibility that PPH may be a *forme fruste* of PH has been raised by some authors. It is intriguing to note, for example, the reports of two instances of PPH in mothers whose offspring suffered with PH.[18, 19] In reviewing the pedigrees, McKusick [20] commented:

"The mode of inheritance is probably autosomal (that is, nonsex-linked) dominant. However, in the pedigrees available to us, sex-linked dominant inheritance cannot be excluded. Specifically in the pedigree reported here and in those previously reported, male-to-male transmission has not been observed. The inheritance might, therefore, be comparable to that of

vitamin D-resistant rickets (hypophosphatemic rickets) in the large kindred studied by Winters and his colleagues.[17] In that instance, although superficially the inheritance suggested an autosomal dominant trait, the consistent failure to observe male-to-male transmission pointed to sex-linked dominant inheritance." [20]

Summary and Conclusions

We have reported the cases of three patients, a mother and two sons, who exhibit skeletal and physiognomonic characteristics suggestive of PPH. An additional six cases, all first and second cousins of our patients, are included in this report, making a total of nine cases in one kindred. None of these six subjects was examined by the authors, but they were described as having body habitus and bony growths similar to those of our patients.

In reviewing the heterogeneous group of cases reported in the literature under the category of PPH, one is forced to conclude that the entity needs not only clearer diagnostic definition but also a change in nomenclature. It is suggested that x-ray skeletal studies of relatives of patients with PH and PPH might be fruitful in bringing to light new cases of familial dyschondroplasia.

Acknowledgment

The authors are deeply indebted to Dr. Victor A. McKusick, Professor of Medicine, Johns Hopkins University School of Medicine, for review of the family pedigree and his comments regarding the mode of genetic transmittance.

Summario in Interlingua

Es reportate le casos de tres patientes, un matre e duo filios, qui exhibiva characteristicas skeletic e physiognomonic supportante le suspicion de pseudo-pseudohypoparathyroidismo. Sex casos additional—omnes concernente prime e secunde cosinos de nostre patientes—es includite in le reporto, de maniera que le total del casos in iste consanguineitate amonta a novem. Nulle del sex subjectos additional esseva examinate per le autores mesme, sed ille sex esseva describite per alteros como habente un habito corporee e un crescentia de osso simile a illos de nostre tres patientes.

In revistar le gruppo heterogenee de casos reportate in le litteratura sub le designation de pseudo-pseudohypoparathyroidismo, on se senti fortiate a concluder que iste entitate require non solmente un plus precise definition diagnostic sed etiam un modification del nomenclatura. Es suggerite que studios radiologic del skeletos de consanguineos de patientes con pseudohypoparathyroidismo e con pseudo-pseudohypoparathyroidismo va possibilemente esser de valor per resultar in le discoperta de nove casos de dyschondroplasia familial.

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IDENTIFICATION OF URATE CRYSTALS IN GOUTY SYNOVIAL FLUID*

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URATE crystals have been noted in synovial fluid from gouty patients in the past, but this finding was believed to be infrequent and of little assistance to the clinician in his attempt to establish a diagnosis.[1] Recently one of us [2] reported that eight of 17 fluids from the affected joints of patients with clinical gout contained crystals seen by ordinary light microscopy, and in several of these cases the diagnosis of gout was first established on the basis of this finding.[2] It was noted that urate crystals in joint fluid were often short and rod-shaped, with rounded ends and parallel sides (Figure 1A), as compared to the long needle-like crystals seen in tophaceous material. Occasionally some crystals appeared broken, possibly as a result of the "mortar and pestle" action of joint motion.

Also described was another type of particle from the synovial fluid of patients with degenerative joint disease (Figure 1B). These particles were called "fibrils" in the belief that they represented desquamated fibrils of cartilage suspended in synovial fluid. They were felt to be akin to those larger and better known inhabitants of synovial fluid termed "joint mice," in that both are derived from cartilage and both are nourished by the surrounding fluid. These particles could be distinguished from urate crystals by morphologic criteria, but they might confuse an observer unaware of their existence. Their darker appearance as noted under ordinary light microscopy, the lack of parallel sides, and the frequently branched and frayed ends clearly distinguish them from urate crystals.

The present study of the synovial fluid obtained from all patients in our clinic with proved or suspected gout was undertaken in order to determine the frequency of occurrence of crystals in gouty synovial fluid, and also to prove that the particles were composed, in all instances, of urate. The murexide test had been employed by one of us (J. L. H.) in the past in an attempt to prove this, but it was unsuccessful due to the small number of crystals present and the interference with the reaction by the protein material of the synovial fluid.

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In addition to inspection of the fluid by ordinary light microscopy, inspection by polarized light microscopy was employed. A uricase digestion test was also devised and performed on all crystals seen in order to determine whether they could be specifically destroyed.

Materials and Methods

Synovial fluid was removed from the affected joints of 18 patients with clinically proved or suspected gout encountered by us within the past year. There were four patients with tophaceous gout and 14 patients with no clinical or radiologic evidence of tophi. Nine of the fluids were obtained during the acute attack and six were obtained from effusions which persisted without symptoms after an acute attack had subsided. Three samples were obtained from chronic tophaceous joints. Material was obtained from the

A

Fig. 1. (A) A representative group of urate crystals in a random drop of synovial fluid by ordinary light microscopy (1,200 ×). Note the characteristic short rod shape, the parallel sides, and the rounded ends.[2]

B

Fig. 1. (B) A representative group of "fibrils" from a random drop of synovial fluid from an osteoarthritic knee (1,200 ×). Note the darker appearance, the lack of parallel sides, and the branched and frayed ends.[2]

bunion joint in six cases, and from the knee in 10 others. The elbow joint and the prepatellar bursa were other sites from which fluid was removed for study. The amount of fluid obtained ranged from 0.2 ml. to 30 ml. The gross appearance of the fluid varied from clear amber to bloody, but in most cases it was an opaque yellow. In three cases of tophaceous gout the fluid appeared milky.

Polarized Light Microscopy: A Zeiss GFL Pol-microscope was used with a first order red plate compensator in place in order to determine the sign of birefringence. A random drop of fluid was placed on a glass slide and inspected at magnifications of 100 ×, 250 ×, and 500 × for the presence of crystals. It seemed more convenient not to use a coverslip; we preferred a thicker preparation through which one could focus up and down looking for crystals. The urate crystals of synovial fluid were found to be nega-

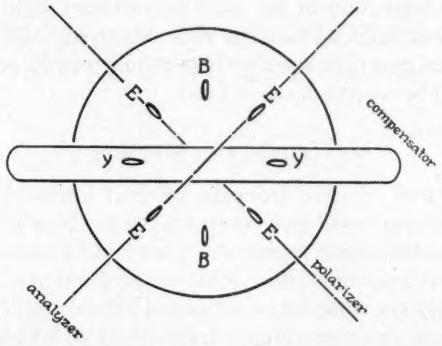

FIG. 2. (A) Diagram of the appearance of a single urate crystal in various positions as the mechanical stage of the polarizing microscope is rotated. The first order red plate compensator is inserted between the crossed nicol prisms in order to determine the sign of birefringence. It causes the background to appear red. When the crystal is at right angles to the direction of slow vibration of light through the compensator (here labled "compensator") it appears blue (B); when it is parallel it appears yellow (Y); and when it lies on the axis of the polarizer or the analyzer it takes on the color of the background, i.e., it is extinct (E). Thus, urate crystals are negatively birefringent and extinguish on the axis.*

FIG. 2. (B) Urate crystals in the synovial fluid from a gouty knee seen by polarized light (500×). This was an exceptionally heavily laden specimen. In most cases only a few crystals could be seen in a given field. The crystals lying at right angles to the plane of slow vibration of light through the compensator appear blue, and those that are parallel appear yellow. Those that are lying on the axis of the polarizer or analyzer are the same color as the background (extinct).

* For a fuller discussion of polariscopic technic, the reader is referred to *Handbook of Chemical Microscopy* by Chamot, E. M., and Mason, C. W., 2nd Ed., Vol. 1, pp. 261–326, John Wiley and Sons, Inc.

tively birefringent with extinction on the long axis (Figures 2A, 2B). Crystals obtained from a subcutaneous tophus had identical optical properties by polarized light.

Uricase Digestion Test: One part of a 1:10 uricase (purified suspension, Worthington Biochemical Corporation—minimal activity, 0.75 units per ml.) dilution in saline was added to five parts of joint fluid. The amount of synovial fluid employed was usually 0.5 ml., but when only very small quantities were available, aliquots as small as 0.05 ml. were successfully used. A quantity of saline, equal in volume to the uricase solution added to the test sample, was added to a control aliquot of synovial fluid. The

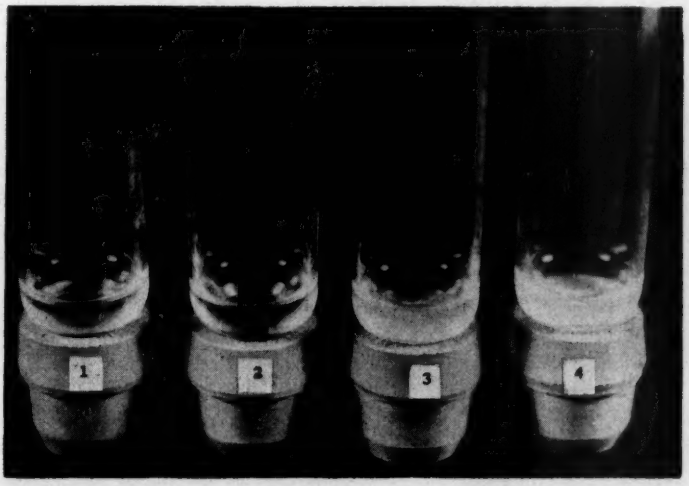

FIG. 3. The uricase digestion test. An aliquot of 0.5 ml. of turbid gouty joint fluid containing numerous crystals by both ordinary and polarized light microscopy was added to each of four tubes. To tube 1 0.1 ml. of a 1:10 uricase dilution in saline was added, while the same amount of 1:100 and 1:1,000 dilution was added to tubes 2 and 3, respectively, and an equal amount of saline was added to control tube 4. After four hours' incubation at 45° C. no crystals were found in tube 1 by either microscopic technic. Tube 2 was cleared completely of crystals in 48 hours, while the crystals in tubes 3 and 4 were not noticeably affected.

tubes were then incubated at 45° C. in a waterbath for four hours.[3] This was the time found necessary to clear the most heavily laden specimen that we had encountered (Figure 3). A random drop from each tube was then placed on a glass slide and inspected by polarized light for the presence of crystals. The pH of the fluids subjected to uricase digestion ranged from 7.8 to 8.1. (The pH readings were not determined anaerobically and are therefore not representative of the in vivo pH of the fluid.)

Ordinary Light Microscopy: A random drop of synovial fluid (usually examined while still warm) was placed directly on a glass slide from the aspirating syringe and was examined under the low and high dry objectives

of an ordinary light microscope. Again no coverslip was used as the thick preparation aided in the rapidity of identification, the principle involved being much the same as the use of thick blood smears when searching for malarial parasites.

Results

Crystals were seen by polarized light microscopy in 15 of the 18 samples, an overall frequency of identification of 89%. Crystals were seen in all four specimens obtained from the joints of patients with tophaceous gout and in 11 of 14 fluids taken from the joints of patients with no clinical or radiologic evidence of tophi. Eight of nine specimens obtained during the acute attack were positive for urate crystals.

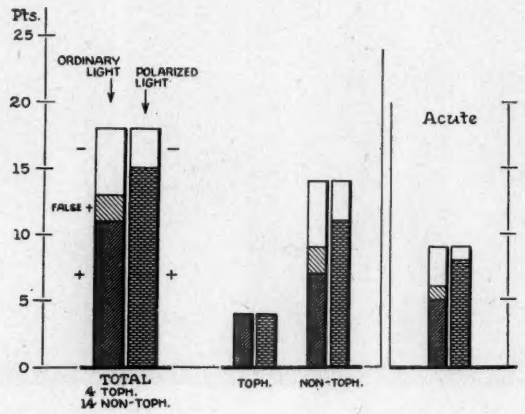

Fig. 4. A graphic comparison of the results of crystal identification by ordinary light microscopy and polarized light microscopy. Note that both false negative and false positive identifications occur by ordinary light microscopy alone.

The results of the uricase digestion tests performed on the 15 specimens which were positive when viewed under polarized light revealed that in all instances the crystals were destroyed. However, crystals could not be re-identified in two of the controls. Apparently heating of the sample to 45° C. and the mild dilution involved in the procedure were enough to dissolve the crystals in these two samples.

Inspection by ordinary light microscopy revealed crystals in 13 of the 18 specimens. Fluids obtained from all four tophaceous cases and nine of 14 fluids obtained from nontophaceous cases were positive for crystals.

When the results by polarized light microscopy were compared with the observations by ordinary light it became obvious that some false positives and false negatives were obtained with ordinary microscopy alone

(Figure 4). True positive identification of urate crystals was raised from 61% to 83% when the polarized light technic was added.

Of special interest were the two false positive identifications made by ordinary microscopy. One such identification was made on a specimen from a 70-year-old Negro male who suffered an acute postoperative arthritis of both knees which responded to colchicine therapy within 48 hours (Figure 5A). The patient, who was operated upon under local anesthesia, described the onset of pain in his knees while he was still on the table. Fluid withdrawn from both knees contained numerous crystals that did not refract polarized light and were not digested by uricase. A year earlier he had experienced a similar attack in both knees following a herniorraphy performed at another hospital. His serum uric acid levels were consistently in the high normal range.

A

FIG. 5. (A) A typical crystal (1,800 ×) by phase contrast microscopy from a knee which appeared to be the site of an acute gouty attack. This crystal did not refract polarized light and was not digested by uricase.

B

FIG. 5. (B) A typical crystal (1,800 ×) by phase contrast microscopy from the knee of a patient who appeared to have "atypical" osteoarthritis. Both knees are aspirated once a month in our clinic and examination has never failed to reveal numerous crystals which do not refract polarized light and are not digested by uricase.

The second false positive identification of "crystals" by ordinary light was in a fluid from a 71-year-old Negro male who had been diagnosed clinically as having an atypical osteoarthritis of both knees and both shoulders. By ordinary light the particles seemed typical of urate but were not birefringent by polarized light and were not digested by uricase (Figure 5B).

DISCUSSION

Even very small crystals could be easily identified under the polariscope by the characteristic flashing color change from blue to yellow and back again as the mechanical stage holding the specimen was rotated. Examination of over 50 fluids from patients with rheumatoid, degenerative, or traumatic arthritis revealed no other particles which were negatively birefringent by

polarized light microscopy. Six fluids from hyperuricemic patients with coincidental joint effusions due to rheumatoid or degenerative arthritis contained no crystals even when the specimen was concentrated by evaporation on the slide. The finding of urate crystals in joint fluid probably has the same diagnostic significance as the finding of a tophus.

The tophaceous cases had, as expected, a higher serum urate level than patients with nontophaceous gout (average, 8.95 mg.%), and also a universally positive identification for synovial fluid urate crystals. The average serum urate level of the nine nontophaceous cases who showed crystals in their joint fluid was 7.4 mg.%, while that of the three without crystals was 6.28 mg.%. The difference in this small series is not significant.

It was previously found by most workers that the urate concentration of the synovial fluid in gout was approximately that of a protein-free filtrate of serum.[4, 5] Kling, however, felt that the urate concentration of the synovial fluid was significantly higher than that of the serum during the acute attack.[6] It may be presumed from our work that the synovial fluid concentration of urate is increased over that of the serum in gouty arthritis by that amount which exists in crystalline form.

Whether or not these particles are causally related to the acute gouty attack is unknown. We have seen such crystals in large numbers in asymptomatic effusions which persist after an acute attack has subsided. The origin and fate of the crystals remains a mystery. They may be formed in the synovial fluid *de novo* or perhaps may form within the synovial lining cells, gaining access to the fluid upon rupture of the cell wall. Certainly in some instances the crystals may be resorbed and in others may maintain a saturated solution of urate in the synovial fluid of higher urate concentration than in the more acidic cartilage. The concentration gradient may lead to the formation of the crystals that are seen just beneath the cartilage surface in histologic sections of autopsy material.

These rapid, simple procedures have been of great clinical value to us in that they provided the initial lead in making the diagnosis in four of the 18 patients encountered, and provided supporting evidence for the clinical diagnosis in all nontophaceous cases. While polariscopic examination is more accurate, observation by ordinary light microscopy is also very rewarding and should be attempted on aspirated fluid whenever the diagnosis is in doubt. Combining the observations by ordinary light microscopy in this series with those by the same technic previously reported [2] reveals that crystals were seen in 23 of 32 fluids from the affected joints of patients with gout. Sixteen of 25 fluids obtained from nontophaceous patients were positive, while all seven specimens from tophaceous cases showed crystals.

The finding of definitely nonurate crystals in the joint fluid from an otherwise clinically typical case of acute gouty arthritis even suggests the possibility of a hitherto unrecognized metabolic abnormality which can mimic the syndrome of gout.

Since it is important to make the diagnosis of this most treatable disease in the field of arthritis with some degree of certainty, aspiration of gouty joints with microscopic examination of the synovial fluid for crystals, by a polarizing microscope if possible, should become a standard diagnostic procedure.

Summary

1. Urate crystals in synovial fluid and the crystals from a subcutaneous tophus were found to have identical optical properties by polarized light microscopy. They were negatively birefringent with extinction on the long axis.

2. Urate crystals were identified by polarized light microscopy in the aspirated synovial fluid obtained from 15 of 18 patients with clinical gout.

3. The crystals were specifically digested by uricase in all 15 samples and in two instances disappeared in the control specimens as well.

4. Urate crystals were also identified by ordinary light microscopy in 11 of the same 18 synovial fluid samples.

5. Comparison of the results of ordinary light microscopy with those seen by polariscopic observation revealed that the percentage of positive identification was greater when the latter method was used. In two instances, crystals were seen by ordinary light which did not have the characteristics of urate crystals. One of these was from an otherwise typical case of acute gouty arthritis.

6. The concentration of urate in the synovial fluid during the acute attack is probably higher than that found in the serum.

Acknowledgments

We wish to thank Dr. Robert E. Hughes, Assistant Professor of Chemistry, Harrison Department of Chemistry, University of Pennsylvania; and Dr. Paul B. Green, Assistant Professor of Botany, University of Pennsylvania, for their helpful suggestions and assistance in the use of the polarizing microscope.

Summario in Interlingua

Liquido synovial esseva prendite ab le afficite articulationes de 18 patientes con clinicamente demonstrate o suspecte gutta, vidite per le autores in le curso de un anno. Le examine microscopic del liquido produceva le sequente resultatos.

1. Esseva trovate que le crystallos de urato in liquido synovial e le crystallos ab un topho subcutanee habeva identic proprietates optic in microscopia a lumine polarisate. Illos esseva negativemente birefringente, con extinction in le axe longe.

2. Crystallos de urato esseva identificate per microscopia a lumine polarisate in le aspirate liquido synovial prendite ab 15 de 18 patientes con gutta clinic.

3. Le crystallos esseva specificamente digerite per uricase in omne le 15 specimens; in duo casos illos dispareva etiam in le specimens de controlo.

4. Crystallos de urato esseva etiam identificate per microscopia a lumine ordinari in 11 del mesme 18 specimens de liquido synovial.

5. Le comparation del resultatos obtenite per microscopia a lumine ordinari con le resultatos obtenite per microscopia a lumine polarisate revelava que le procentage

del identificationes positive esseva plus alte quando le secunde del duo mentionate methodos esseva usate. In duo casos, crystallos esseva vidite in lumine ordinari le quales non habeva le characteristicas de crystallos de urato. In un de istos, il se tractava de un alteremente typic caso de acute arthritis guttose.

6. Le concentration de urato durante un attacco acute es probabilemente plus alte in le liquido synovial que in le sero.

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HYPOGONADISM IN YOUNG MEN (WITH EMPHASIS ON KLINEFELTER'S SYNDROME) * †

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SIGNIFICANT advances have recently been made in our understanding of sexual differentiation and maturation. Reports on the application of this knowledge to the differential diagnosis of hypogonadism in the male have been essentially limited to the study of patients who presented themselves for examination because of infertility. In this paper we present an evaluation of a large number of young men with sexual underdevelopment manifested by eunuchoidism, gynecomastia, or small testes. An attempt has been made to establish the incidence of such aberrations and to analyze intensively their nature. Of particular significance has been the discovery of Klinefelter's syndrome in a large proportion of subjects with findings of hypogonadism. Because of the current interest in Klinefelter's syndrome and its frequency of appearance in our series, additional consideration has been given this form of hypogonadism, and an effort has been made to explain its pathophysiology in view of recent findings.

MATERIALS AND METHODS

The subjects of the present report were obtained from 72,146 male recruits examined at the Medical Processing Unit on this base during a 12-month period beginning June 1, 1959. The majority of these recruits were 17 to 19 years of age; the remainder were in their early twenties. Each had received a preinduction physical examination, and some degree of prior selection was therefore unavoidable. However, hypogonadism is not, in itself, cause for nonacceptance for military duty, unless psychological disturbances are manifest. All recruits were briefly examined in the nude by a medical corpsman who had been instructed to refer those with small testes, eunuchoidism, or sexual underdevelopment to the Endocrine Clinic. Those with only gynecomastia were excluded from this report.

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In addition, 1,000 consecutive recruits were examined at random by one of the authors, in an attempt to determine more exactly the incidence of the various types of hypogonadism in young male adults.

The following examinations were performed on the patients who were referred to the Endocrine Clinic:

1. *Smears for Chromatin Staining.* Slides of cells scraped from the buccal mucosa were prepared by the method of Moore and Barr.[1] At least 100 cells were examined for chromatin bodies; those identified as negative had less than 5% with the chromatin body, whereas the positive had over 40%.

2. *Testicular Biopsy.* Tissue removed from both testes by open biopsy was fixed in modified Bouin's solution and stained with hematoxylin and eosin.

3. *Semen Analysis.* Only about one-half of the subjects were able to produce an ejaculum. The fluid was microscopically examined for sperm.

4. *Urinary Ketosteroid Excretion.* Aliquots of 24-hour urine specimens were analyzed by the Drekter modification[2] of the Zimmerman technic, which yields as a normal range in young adults an excretion of from 8 to 22 mg./24 hrs. Chromatographic fractionation of the ketosteroids was performed in the majority of the subjects, and, in some, was repeated after the administration of testosterone, ACTH, chorionic gonadotropin, or SU-4885. These studies will be the subject of an additional report.

5. *Urinary Gonadotropin Excretion.* After preparation of the urine by the technic described by Albert,[3] assays were performed, using as a criterion the increase in weight of the mouse uterus. Excretion in normal young males varied between 6 and 25 M.U./24 hrs.

6. *Intelligence Quotients.* Standard Armed Forces I.Q. and aptitude examinations were converted to I.Q. equivalents of the modified Stanford-Binet tests. Individual Stanford-Binet and Wechsler-Bellevue tests were also performed on 16 of the subjects. An I.Q. of less than 70 is unacceptable for Air Force duty.

7. *Color Vision.* This was determined by use of AO Pseudo-Isochromatic Plates.

Results

Incidence: Among the 1,000 consecutive young men examined at random, 14 had bilateral gynecomastia, four had delayed puberty, and two had testes less than 2 cm. in length. Both of these latter subjects were found to have chromatin-positive Klinefelter's syndrome.

Of the entire group of new recruits, only those with the more apparent hypogonadism were referred to us for study. The majority of the less obvious cases were undoubtedly missed. If the incidence of Klinefelter's syndrome found in the entire group were comparable to that found in the 1,000 consecutive recruits examined, well over 100 cases of this form of hypogonadism should have been recognized.

Classification: In Table 1, a classification of hypogonadism is given, together with the frequency of each diagnosis revealed in our total series.

Clinical Findings: Tables 2 and 3 detail pertinent physical characteristics, laboratory studies, and biopsy findings in each patient studied. Buccal smears for nuclear chromatin, done on all patients, were positive only in cases 15 through 31. No spermatozoa were found in the seminal fluids

obtained. Color vision was normal in the 12 of the 17 patients with chromatin-positive Klinefelter's syndrome tested.

I. *Delayed Adolescence.* Of 14 cases of delayed adolescence seen, two were studied in detail because of slight micro-orchidism. Nevertheless, theirs were the largest testes seen in the series. Physically, as is illustrated by the patient in Figure 1A, they resembled prepubertal individuals without gynecomastia or eunuchoidism. Gonadotropin and ketosteroid levels were in the range seen during early adolescence. Testicular biopsy showed normal architecture with active spermatogenesis (Figure 1B).

II. *Hypothalamic Lesions.* No examples of these rare conditions were uncovered.

III. *Pituitary Deficiency.* A. Panhypopituitarism. Our patient had no overt clinical evidence of pituitary deficiency except hypogonadism. The

TABLE 1

Classification of Hypogonadism in the Male

	No. Cases Seen*
I. Delayed adolescence	14
II. Hypothalamic lesions	0
A) Sexual infantilism without obesity	
B) Sexual infantilism with obesity	
1) Froelich's syndrome	
2) Laurence-Moon-Biedl Syndrome	
III. Pituitary deficiency	
A) Generalized	1
B) Isolated gonadotropin deficiency	2
IV. Testicular deficiency	
A) Acquired	4
B) Germinal aplasia	2
C) Klinefelter's syndrome	
1) Chromatin-negative	3
2) Chromatin-positive	17

* Incidence in 72,146 recruits.

degree of maturity evident in both the physical examination (Figure 2A) and the testicular biopsy (Figure 2B) may be attributable to a series of "hormone shots," thought to be chorionic gonadotropin, administered at age 16. Skull films and the neurological examination were normal, but the bone age was retarded. Thyroid function was depressed, with a protein-bound iodine of 3 μg.% and a 24-hour I^{131} uptake of 7.6%. The uptake increased to 19.2% after 30 units of thyroid-stimulating hormone were administered over a three-day period. Adrenal function was also initially low, with a 24-hour urinary hydroxycorticoid value (Porter-Silber chromogen) of 1.8 mg., which rose to 7.4 mg. after three days of intramuscular ACTH, 40 units daily. Pituitary ACTH production was considered deficient on the basis of a subnormal response to the intravenous infusion of

TABLE 2—Clinical and Laboratory Data on Hypogonadal Men

Case #	Age	Body Type	Gynecomastia	Phallus	Testicles (Length in Cm.)	17-KS (mg./24 hr.)	FSH (M.U./ 24 hr.)	I.Q.
I. Delayed Puberty								
1. C.W.	18	Immature	None	Sl. small	3.5	6.3	10	73
2. T.W.C.	17	Immature	None	Sl. small	3.0	8.0	12	84
III. Hypopituitarism								
A. Panhypopituitarism								
3. A.D.M.	20	Eunuchoid	None	Sl. small	2.0	6.4	<2.5	83
B. Gonadotropin deficiency								
4. C.E.U.	19	Eunuchoid	None	Infantile	1.0	4.7	<5.	99
5. J.L.P.	25	Normal	None	Mod. small	2.5	7.0	<10.	100
IV. Testicular deficiency								
A. Acquired								
6. L.L.B.	17	Eunuchoid	None	Infantile	2.0	4.7	36	108
7. R.C.McD.	20	Eunuchoid	Slight	Infantile	Not palpable	9.9	88	118
8. C.E.R.	18	Eunuchoid	None	Sl. small	1.5	5.3	112	93
9. J.A.McC.	20	Eunuchoid	None	Mod. small	Not palpable	3.6	64	150
B. Germinal cell aplasia								
10. R.Z.	20	Normal	None	Normal	1.5	10.2	60	—
11. R.L.H.	18	Normal	None	Normal	2.5	12.6	31	—
C. Klinefelter's: chrom. neg.								
12. J.O.S.	19	Normal	None	Normal	1.5	8.8	80	118
13. R.L.G.	20	Normal	None	Mod. small	1.5	3.5	>96	103
14. J.W.	22	Eunuchoid	Slight	Mod. small	2.0	7.6	50	—
Klinefelter's: chrom pos.								
15. J.J.B.	23	Eunuchoid	Marked	Normal	1.5	21.9	98	91
16. J.D.C.	21	Eunuchoid	Marked	Mod. small	1.0	22.6	200	95
17. J.J.E.	19	Eunuchoid	None	Mod. small	1.0	14.6	160	102
18. H.B.W.	18	Eunuchoid	Moderate	Mod. small	1.5	6.7	>100	—
19. K.A.W.	18	Eunuchoid	Marked	Mod. small	0.5	17.8	89	92
20. M.D.R.	18	Normal	None	Normal	1.0	30.0	176	95
21. K.A.S.	19	Eunuchoid	Moderate	Mod. small	1.5	17.2	42	80
22. P.T.McG.	22	Eunuchoid	Slight	Mod. small	1.0	35.0	308	97
23. M.F.H.	20	Eunuchoid	Moderate	Mod. small	0.5	8.1	48	102
24. F.R.VanH.	19	Eunuchoid	None	Mod. small	1.5	6.1	>50	—
25. R.C.D.	17	Eunuchoid	Marked	Normal	2.0	20.6	120	116
26. D.W.B.	19	Eunuchoid	Moderate	Infantile	1.0	5.8	169	114
27. C.V.R.	18	Normal	Slight	Normal	1.0	12.7	120	94
28. F.L.B.	23	Normal	Slight	Normal	Prosthesis	12.3	120	106
29. K.V.N.	20	Normal	Slight	Normal	1.0	23.2	115	101
30. E.M.O.	18	Eunuchoid	None	Sl. small	0.8	11.9	160	99
31. W.M.N.	18	Normal	None	Normal	2.0	8.4	80	106

the 11-beta-hydroxylase inhibitor, SU-4885. This agent diminishes hydrocortisone synthesis, leading, in the normal subject, to an increased release of ACTH as reflected in a rise in the production of other adrenal hormones, measured as 17-ketogenic steroids (KGS).[4] The response to 30 mg./Kg. body weight given over a four-hour period to both normal subjects and patients with hypogonadism due to various primary testicular diseases is a doubling of KGS excretion.[5] Our patient's control KGS levels were 1.1 mg. in 12 hrs., and 2 mg in 24 hrs. After SU-4885, excretion rose to only

TABLE 3

Testicular Biopsies of Subjects with Hypogonadism

Case #	Tubule Size	% Fibrosed Tubules	Spermatogenesis	Leydig's Cells
I. Delayed Puberty				
1. C.W.	Normal	None	Normal	Normal
2. T.W.C.		Not done		
III. Hypopituitarism				
A. Panhypopituitarism				
3. A.D.M.	Small	None	None	None
B. Gonadotropin deficiency				
4. C.E.U.	Small	None	None	None
5. J.L.P.	Normal	None	Partial	None
IV. Testicular Deficiency				
A. Acquired				
6. L.L.B.		Not done		
7. R.C.McD.	Small	None	None	Increased
8. C.E.R.	Normal	20	Partial	Sl. increase
9. J.A.McC.		No testicular tissue found		
B. Germinal cell aplasia				
10. R.Z.	Normal	None	None	Sl. increase
11. R.L.H.	Normal	None	None	Normal
C. Klinefelter's: chrom. neg.				
12. J.O.S.	Normal	95	None	Sl. increase
13. R.L.G.	Normal	40	None	Sl. increase
14. J.W.		Performed elsewhere		
Klinefelter's: chrom. pos.				
15. J.J.B.	Small	70	Partial	Marked increase
16. J.D.C.	Small	70	None	Marked increase
17. J.J.E.	Small	60	None	Mod. increase
18. H.B.W.	Small	99	None	Marked increase
19. K.A.W.	Small	50	None	Marked increase
20. M.D.R.		Not done		
21. K.S.A.	Small	90	None	Marked increase
22. P.T.McG.	Small	80	None	Marked increase
23. M.F.H.	Small	60	None	Mod. increase
24. F.R.VanH.	Small	60	None	Marked increase
25. R.C.D.	Sl. small	50	None	Mod. increase
26. D.W.B.	Small	95	None	Marked increase
27. C.V.R.	Small	90	None	Mod. increase
28. F.L.B.		Performed elsewhere		
29. K.V.N.	Small	95	None	Marked increase
30. E.M.O.	Small	90	None	Marked increase
31. W.M.N.	Normal	50	Complete	Sl. increase

1.4 mg. in 12 hrs. and 2.4 mg. in 24 hrs. Testicular biopsy showed incomplete maturation of the tubules and the absence of Leydig's cells (Figure 2B), reflecting a deficiency of follicle stimulating hormone (FSH) and interstitial cell stimulating hormone (ICSH), respectively.

B. Isolated Gonadotropin Deficiency (Idiopathic Eunuchoidism with Low FSH, Hypogonadotrophic Eunuchoidism). The variation in the physical appearance of our two patients reflects the difference in the time of onset of gonadotropin deficiency. In case 4, gonadotropin production had apparently never increased, since secondary sexual development was totally

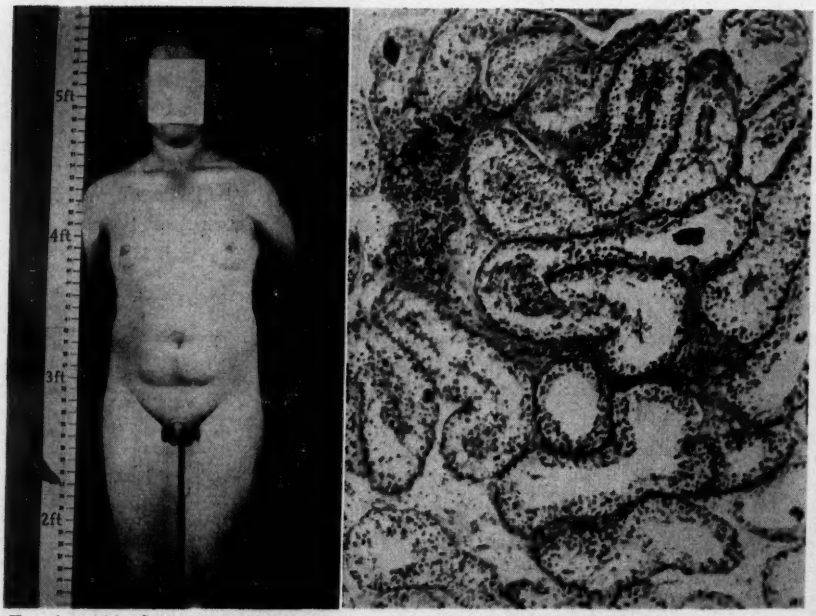


FIG. 1. (A) *Case 1.* Delayed puberty. (B) Testicular biopsy showing maturation of seminiferous tubules with complete spermatogenesis. Leydig's cells are present. × 80.

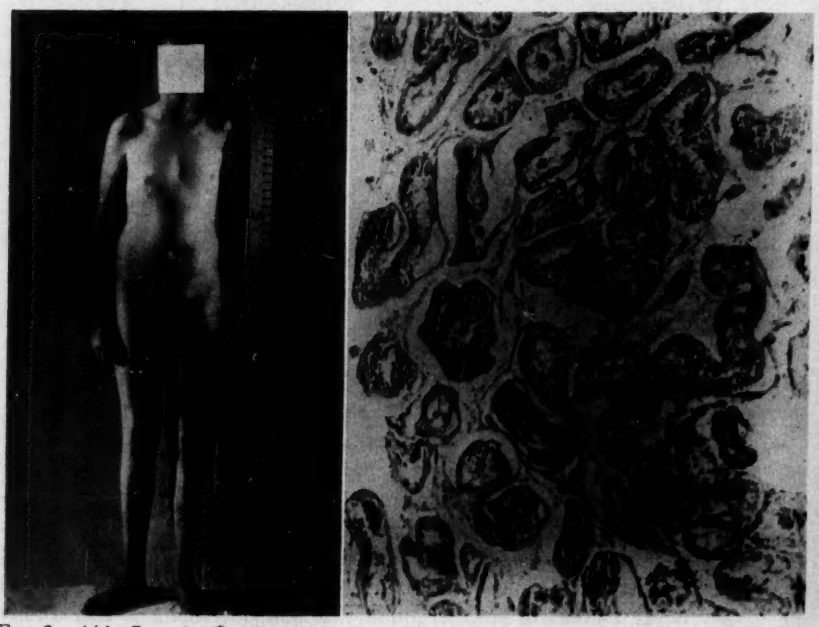


FIG. 2. (A) *Case 3.* Panhypopituitarism. (B) Tubules small, without spermatogenesis. No Leydig's cells are present. × 80.

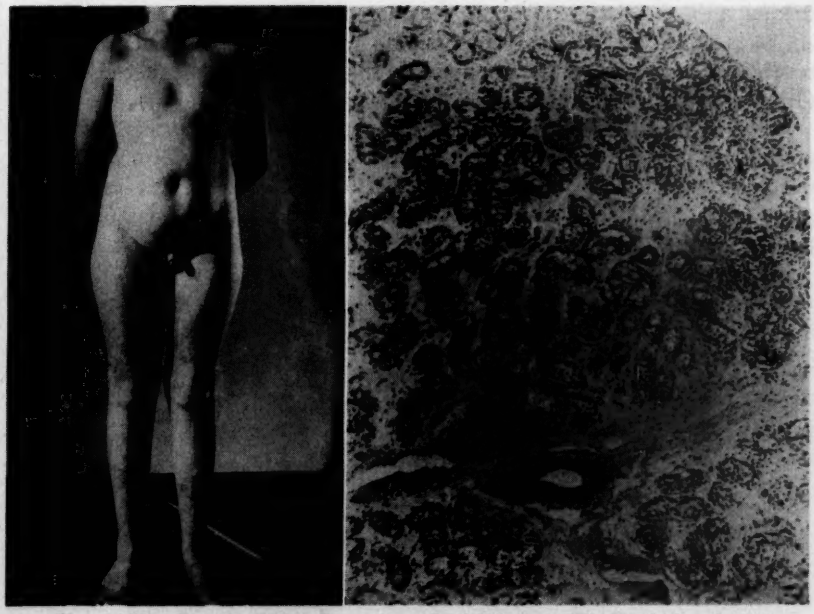


FIG. 3(A). *Case 4.* Isolated gonadotropin deficiency. (B) Testicular tissue markedly immature. × 80.

FIG. 4(A). *Case 5.* Isolated gonadotropin deficiency. (B) Tubules normal in size, but spermatogenesis is deficient and Leydig's cells are absent. × 80.

lacking (Figure 3A). Urinary gonadotropin excretion was diminished, but tests of adrenal and thyroid function were normal. Testicular biopsy revealed a markedly immature architecture, with no Leydig's cells visible (Figure 3B).

Less frequently, gonadotropin deficiency may become manifest after puberty, as in case 5 (Figure 4A). Libido, potentia, and sperm production were repressed but no regression of sexual development was evident. The prior occurrence of gonadotropin secretion accounts for the maturation of tubular architecture seen, whereas the decrease in both sperm production and

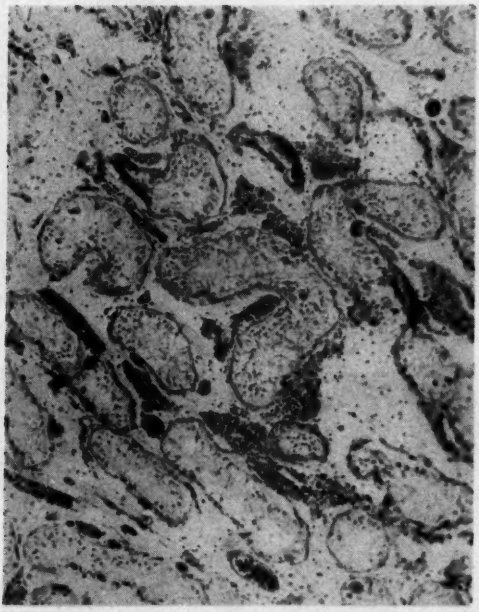


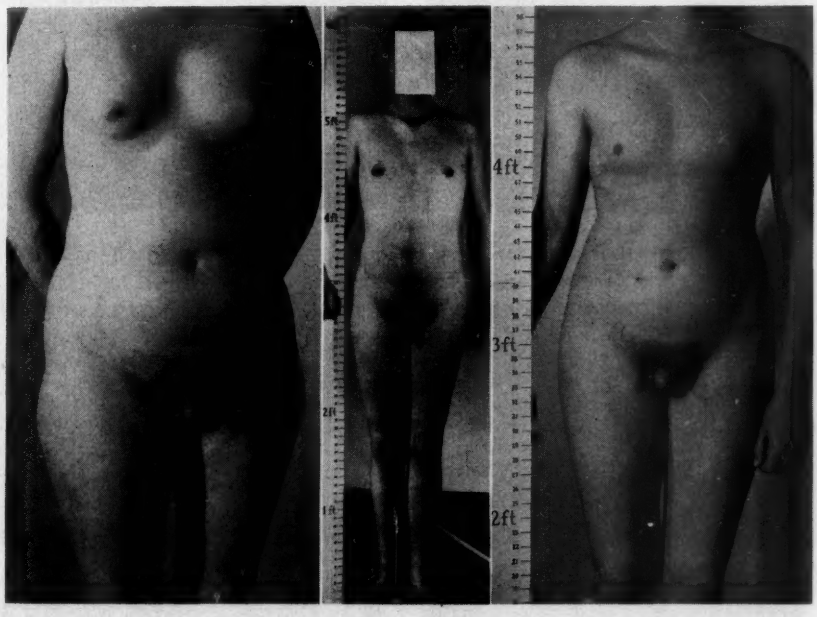
FIG. 5. *Case 10.* Germinal aplasia. Tubules lined only by Sertoli's cells, with no germ cells evident. Leydig's cells not overly prominent. × 80.

the number of Leydig's cells reflects the subsequent deficiency of trophic hormone production (Figure 4B).

IV. *Testicular Deficiency.* A. "Acquired" Defects. The types of insult to which the testes may be subjected are varied and frequently unrecognized, as in case 8. Virtual castration may be accidentally produced by trauma, as in case 6, or by surgical insult, as in case 7. Congenital anorchia may be most conveniently placed under this category for the sake of brevity in classification. Case 9 represents an instance wherein surgical exploration revealed no testicular tissue, although portions of the epididymides were identified.

B. Germinal Aplasia. The patients with this condition had no apparent abnormalities of sexual development other than small testes. The testicular biopsy, as exemplified by that of case 10, revealed the absence of spermatogenic cells within tubules of normal architecture lined only by sustentacular cells of Sertoli (Figure 5). Leydig's cells were not overly prominent.

C. Klinefelter's Syndrome. This diagnosis was made in 20 of 31 subjects seen for hypogonadism. Their body habitus varied from normal to markedly eunuchoidal (Figure 6A, B, and C). Thirteen of the 20 had gynecomastia. As has been emphasized, micro-orchidism may be the only



A B C

FIG. 6(A) (B) (C). Patients with Klinefelter's syndrome. Both A (*case 29*) and B (*case 31*) are chromatin-positive, whereas C (*case 14*) is chromatin-negative.

distinguishing clinical feature. Elevated gonadotropin excretion and a typical, though somewhat varied, testicular pathology were the only other constant findings. Perhaps partly because of prior selection, the intelligence of the group, as determined by objective testing, was not unusual, although the increased frequency of this syndrome among mental defectives has been well substantiated.

The testicular histology of this syndrome is demonstrated in Figure 7. Tubular hyalinization and prominence of Leydig's cells were seen in all biopsy specimens. In general, the chromatin-positive cases had smaller

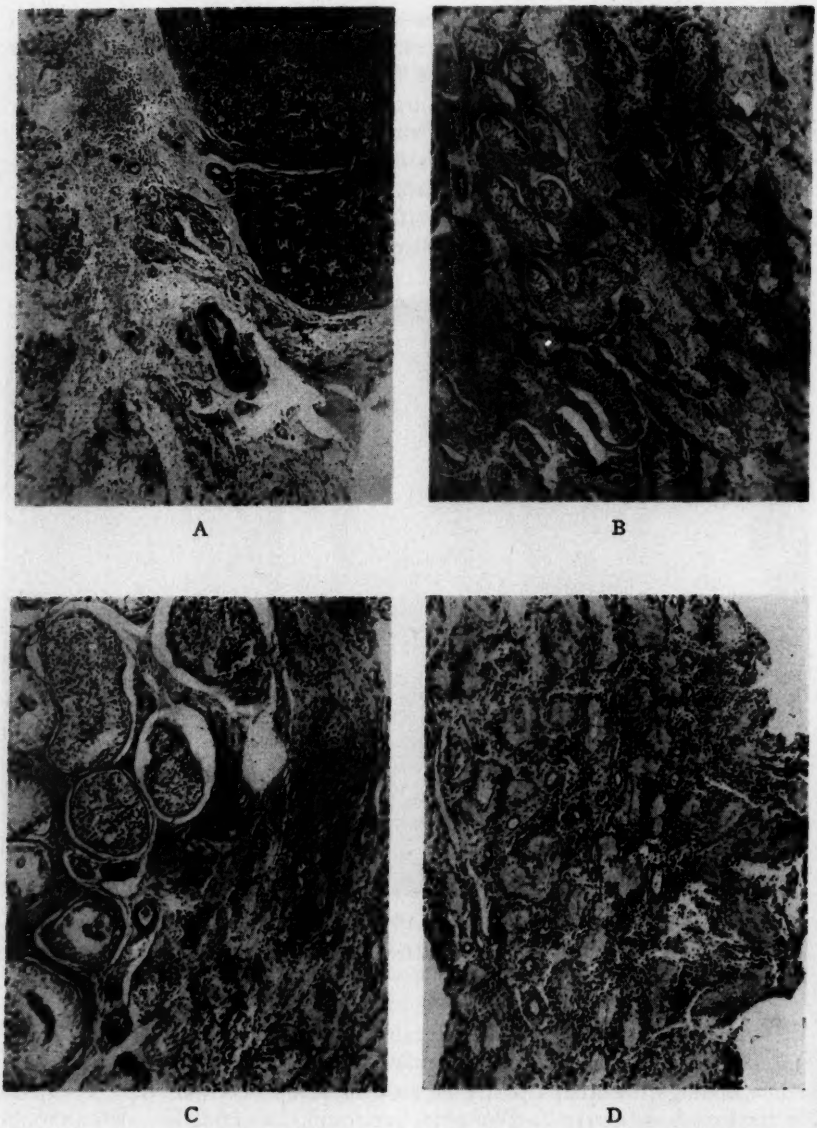


FIG. 7. Testicular tissue in Klinefelter's syndrome. The typical pathologic appearance of chromatin-positive cases is shown in A (*case 29*). Characteristics considered more compatible with the histologic appearance of chromatin-negative cases may also be noted in chromatin-positive patients as is shown in B (*case 17*) and C (*case 31*). In C an area with complete spermatogenesis is evident. Moreover, occasional chromatin-negative patients may show complete fibrosis of uniformly small tubules, as in D (*case 12*). All × 80.

tubules which were more completely hyalinized, and there was more prominent clumping of Leydig's cells (Figure 7A). However, areas with nonsclerosed tubules, quite large and uniformly spaced—a picture considered characteristic of the negative group—were seen in the biopsies of chromatin-positive individuals (Figure 7B), one of whom had an area of complete spermatogenesis (Figure 7C). Moreover, areas with complete sclerosis of uniformly small tubules were found in the tissue of patients with chromatin-negative Klinefelter's syndrome (Figure 7D).

Discussion

The differential diagnosis of hypogonadism in the young male can be made with certainty and relative ease, utilizing the information and technics recently advanced, and studying the pattern of hormonal excretion. Each type of hypogonadism seen, during a one-year period, in recruits referred to us for special duty, will be discussed. Unfortunately, patients with delayed or abnormal sexual development may be either unaware of their condition or not sufficiently concerned to seek medical attention. Only four of our 31 patients had been previously evaluated for hypogonadism. The striking physical and psychological improvement produced by hormonal replacement therapy should prompt all practitioners to seek out and diagnose such cases whenever possible.

I. *Delayed Adolescence.* Puberty may be delayed to age 17 or, rarely, even beyond, and development may then spontaneously begin and progress normally.[6] The differentiation from primary gonadotropin deficiency may be difficult, and may be assured only by the spontaneous occurrence of sexual maturation. Those patients with simple delay of puberty often have a history of similar delay in the family; their appearance is immature, but neither eunuchoidism nor gynecomastia is usually seen. As demonstrated by our two patients, gonadotropin and 17-ketosteroid levels are those of a normal adolescent, and the testicular biopsy shows normal architecture, with varying degrees of maturation and spermatogenesis.

II. *Hypothalamic Lesions.* The frequency of the diagnosis of these conditions has progressively diminished as our knowledge of sexual development and hormonal interrelationships has advanced. That no hypothalamic lesions were found in our series may also reflect the prior screening given our subjects. Caution has been advised in diagnosing these lesions in the absence of the characteristic accompanying defects.[7]

III. *Pituitary Deficiency.* A. Panhypopituitarism. The clinical findings in this condition are dependent upon the time of onset and the degree of pituitary failure. If the onset is in early childhood, dwarfism is usually present. When it develops later in childhood, but before completion of puberty, as in our case, sexual development is impaired and disproportionate growth of the extremities is produced by the delay in epiphyseal closure. When panhypopituitarism supervenes after completion of sexual maturation,

androgenic function diminishes, but only minimal regression of body development occurs.

Emphasis should be given the relative importance of hypogonadism in making this diagnosis. As in our case, gonadal insufficiency may be the first or only clinical evidence of panhypopituitarism. Thyroid and adrenal deficiency may remain clinically inapparent, requiring appropriate hormonal studies for their recognition.

B. Isolated Gonadotropin Deficiency. The reported frequency of this condition, in which no organic lesion can usually be demonstrated, varies from the 62% of 148 eunuchoidal patients seen by Nelson [8] to the 13% incidence in 142 patients with "testicular deficiency" described by Howard.[9] Again, the clinical picture varies with the time of onset. Most frequently, gonadotropin secretion never occurs, so that sexual immaturity persists, as in case 4. Such cases may be difficult to distinguish from instances of delayed puberty. The absence of gonadotropin excretion and the more marked and prolonged physical and histologic immaturity suggest an organic defect rather than mere pubertal delay. When gonadotropin deficiency occurs after a period of normal secretion, as in case 5, the diagnosis becomes more difficult and essentially dependent upon hormonal studies. Such gonadotropin deficiency may be the earliest manifestation of lesions which later produce more complete pituitary hypofunction.

IV. *Testicular Deficiency.* A. "Acquired" Defects. The seminiferous tubules are more susceptible to injury than the Leydig's cells, and infertility without eunuchoidism is the usual result. The nature of our case selection excluded such patients, and the few subjects with these defects who appeared in our series were eunuchoidal. Although an exact etiologic diagnosis may not be evident, mumps orchitis, exposure to radiation, cryptorchidism, and trauma are the more common causes. A special category is the testicular atrophy with marked tubular fibrosis seen in about 80% of males with myotonia atrophica.[10]

B. Germinal Aplasia. This condition, originally described by del Castillo et al.,[11] has been frequently discovered among infertile subjects. The patients are usually apparently normal men, found to have azoospermia and moderate micro-orchidism. The incidence in our series is, therefore, understandably low, and our two cases were discovered only because of the small testes of the subjects. A few individuals with this condition, diagnosed with assurance only by the finding of an absence of germ cells in otherwise fairly normal testicular tissue, have been found to have gynecomastia and eunuchoidism. The etiology remains unknown, although a failure of the primordial germ cells to migrate into the testes has been postulated.[11]

C. Klinefelter's Syndrome. The clinical spectrum encompassed by the diagnosis of Klinefelter's syndrome has progressively enlarged since its recognition in 1942. The original description included gynecomastia, aspermatogenesis in the presence of Leydig's cells, and increased urinary FSH

excretion.[12] Heller and Nelson in 1945 described cases lacking gynecomastia and emphasized the variability of eunuchoidism.[13] They insisted upon the presence of the following "constant" features: (1) small testes, which on biopsy show (a) tubules hyalinized or lined only by Sertoli cells, with failure of spermatogenesis and (b) interstitium with clumped Leydig's cells; (2) azoospermia; and (3) high urinary gonadotropin levels.

The discovery in 1956 [14-17] that most patients with Klinefelter's syndrome have a "female" chromatin pattern offered a simple approach to the diagnosis of this condition and stimulated interest in its study. Thus, of over 650 cases collected from the world's literature, all but 67 were reported after 1956. Of particular significance have been the uncovering of prepubertal cases and the realization that patients may have none of the eunuchoidal features so commonly described in earlier case reports. Moreover, of the criteria presented by Heller and Nelson, the failure of spermatogenesis and azoospermia can no longer be considered invariable. Isolated areas of spermatogenesis were found within the testicular tissue of one of our chromatin-positive cases, and this finding has been noted in at least 38 patients, 12 of whom were forming spermatozoa.[18-29] (Of this total, 27 were chromatin-positive.) The presence of sperm in the seminal fluid is, to be sure, rare, but it has been noted in four chromatin-positive patients reported by Ferguson-Smith et al.[30] and in one individual in Raboch's series.[24]

The frequency of the syndrome in our series of young men with hypogonadism seems surprising. Comparison with other reports is difficult due to variation in patient population. In an older age group studied by Raboch, 31 of 44 men with small testes were found to have the chromatin-positive Klinefelter's syndrome. Other reported incidences of the chromatin-positive group include 0.26% of all newborns,[31] 1:1,000 of all phenotypic males,[32] 1:42 of mental defectives,[32] and about 20% of azoospermic adults.[33] The relative frequency of the chromatin-negative group is much more difficult to determine, but if sampling errors can be minimized, it appears to be about one-third as common as the chromatin-positive group.[23]

In the avalanche of literature written since the discovery of the nuclear chromatin mass in some patients with Klinefelter's syndrome, certain discrepancies have appeared and have caused considerable confusion. First, attempts were made [28, 34, 35] to explain the pathogenesis of this condition on the basis of the animal experiments by Jost on primordial gonadal development.[36] The applicability of these theories relating to cortico-medullary imbalance has been questioned since the demonstration in 1959 of a chromosomal aberration in the chromatin-positive group.[37, 38] The number of chromosomes in the majority of such patients examined has been 47, with two Xs and one Y sex chromosome being present. The etiology of the disease in these subjects appears to be explained by the presence of this abnormal sex chromosome pattern,[39] although two chromatin-positive patients have been found to have only one X and a normal total count of

46.[40] No definite pathogenetic mechanism has been proved for the chromatin-negative group.

Second, a confusing array of names, usually based on the theories of cortico-medullary imbalance, has been given the two types of Klinefelter's syndrome. We prefer simply to divide patients into chromatin-positive and chromatin-negative groups. The term "primary micro-orchidism" currently favored by the British [41] seems misleading since the gonads may be small in other primary testicular disease states.

Third, disagreement has also arisen over the diagnostic criteria for this syndrome. The presence of a positive chromatin smear in a phenotypic male assures the diagnosis,[42] excluding the extremely rare instances of true hermaphrodism. The diagnosis in a chromatin-negative postpubertal patient, however, must be based upon the presence of tubular hyalinization with defective spermatogenesis and prominent Leydig's cells within the tissue obtained by biopsy of scrotal testes. Emphasis should be placed on the scrotal position of the testes since both elevated gonadotropin levels and a testicular pathology similar to that of Klinefelter's syndrome may be noted in testes which have remained undescended for many years.[43] Although the chromatin-positive and -negative groups may be distinguished by the appearance of the testicular tissue,[30] the pathologic differences may overlap (Figure 7).

Doubt has been expressed over the separation of patients in the chromatin-negative group into a distinct entity,[19] with the comment that "they are not readily separable from other men with severely impaired spermatogenesis consequent to tubular fibrosis." [23] Others have included instances of germinal aplasia in series of chromatin-negative Klinefelter's syndrome.[27] The two seem clearly separable on the grounds of distinct pathologic appearances as demonstrated in Figures 5 and 7 and emphasized in the literature.[11, 44] Moreover, there is a much smaller incidence of gynecomastia and eunuchoidism among patients with germinal aplasia.[6, 9, 11, 27] Admittedly a deficiency of germ cells is common to both and some of the seminiferous tubules in the chromatin-negative Klinefelter's may look similar to those seen in germinal aplasia,[25] but tubular hyalinization and Leydig's cell prominence is not seen in the group with aplasia. As originally described and subsequently upheld, the two conditions are distinct and should be so considered.

Last, a few cases of Klinefelter's syndrome have been reported to have normal urinary gonadotropin titers,[16,,22, 23] but the vagaries of this determination may well explain this infrequent discrepancy. The titers were definitely elevated in all of our cases, in most to rather striking levels.

The Pathophysiology of Klinefelter's Syndrome

Despite these disagreements, significant advances in our understanding of Klinefelter's syndrome have appeared. As yet, however, few attempts [23, 45] have been made to interpose this additional information into the

pathophysiologic schemes originally presented. We offer such an attempt (Figure 8) based upon the concepts of Klinefelter et al.[12] Although some of the relationships are speculative and inferential, they are compatible with the facts as we know them.

Basic to this syndrome is a deficiency of germ cells,[23, 29, 41, 46] in the majority of patients related to a genetic aberration, in the remainder produced by factors not yet recognized. Examination of testes from prepubertal cases reveals either an absence or marked decrease of germ cells.[41, 47, 48] Not until the onset of puberty with the secretion of progressively increasing amounts of gonadotropin does the typical tubular hyalinization and sclerosis appear.[32, 41,] A direct correlation between the abnormally

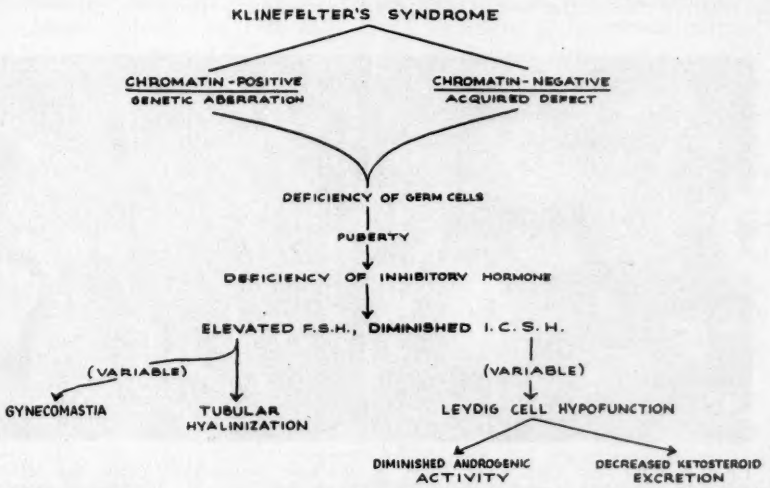


FIG. 8. Schematic representation of the pathophysiology of Klinefelter's syndrome.

increased gonadotropin excretion and the degree of tubular sclerosis has been noted.[49]

The explanation for the increased gonadotropin excretion offered by Klinefelter [12] has been supported by the studies of both McCullagh [50] and Heller [51] and their co-workers. They strongly suggest that germinal cell deficiency leads to an increased excretion of pituitary gonadotropin, as seen not only in Klinefelter's syndrome, but also in other conditions associated with germinal cell damage.[50-54] Deficiency of a second testicular hormone, the "X" substance [12] or "inhibin" [50] supposedly produced by the spermatogenic cells and controlling pituitary gonadotropin secretion, has been postulated to explain the close correlation between deficiency of germinal cells and gonadotropin excess.[50]

Since tubular hyalinization begins only after gonadotropin titers become elevated, the possibility that the excessive gonadotropins may induce the postpubertal tubular degeneration is offered. This cause and effect relationship receives strong support from the studies of Maddock and Nelson, which showed marked degenerative changes in the seminiferous tubules of adults with functioning testes, when they were given chorionic gonadotropin (CGT).[55] These changes, as shown in Figure 9, included basement membrane hyalinization, peritubular fibrosis, necrosis and sloughing of germinal cells. There were no changes seen in Sertoli's cells. Could not high levels of endogenous gonadotropin produce similar and progressive tubular degeneration, as seen in Klinefelter's syndrome? Since laboratory separation of gonadotropins into FSH and ICSH is not generally feasible, the relative role of the two in this process remains speculative. However, it

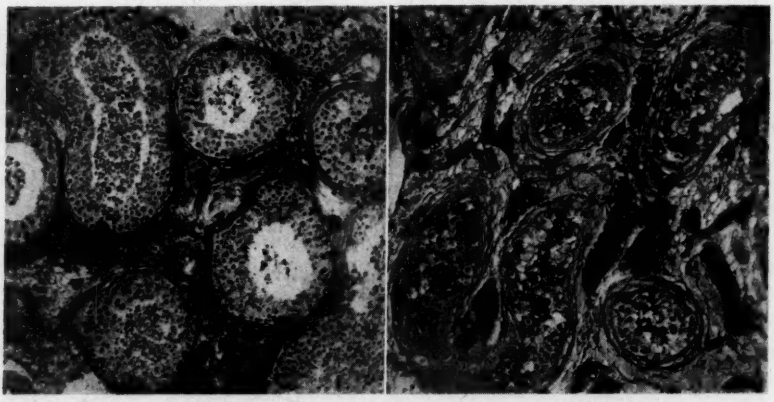


FIG. 9. (A) and (B). The effect of chorionic gonadotropin upon the testicular histology of normal adult men, as shown by Maddock and Nelson.[55] The normal appearance before treatment is shown in A, whereas the marked degenerative changes induced by CGT are demonstrated in B. Reproduced by permission of the publisher.

seems likely that FSH, shown to be present in CGT,[56] would be primarily responsible for both the induced and the naturally occurring tubular degeneration (see below.)

Support for the hypothesis that prolonged exposure of the seminiferous tubules to excessive endogenous gonadotropin may be deleterious is found in observations on cryptorchidism. Here again, tubular fibrosis is noted only after puberty and is associated with elevated gonadotropin titers.[57] Tubular damage in the cryptorchid testis has been attributed to exposure to the higher temperature within the groin.[58] Yet, the tubular architecture remains histologically unaffected by such temperatures until after the onset of puberty and the elaboration of excess gonadotropin. The number of germ cells within the majority of cryptorchid testes is presumably normal

initially,[59] and only slowly diminishes during childhood and adolescence; the process of gonadotropin overproduction with its resultant tubular damage would therefore be more gradual than that seen in Klinefelter's syndrome.

The structure of the scheme presented here is weakened by the absence of progressive tubular hyalinization in association with elevated gonadotropins in patients with germinal aplasia. Other theories [23] for the pathophysiology of Klinefelter's syndrome must also face this enigma, and suffer from it just as has ours.

The appearance and function of Leydig's cells in Klinefelter's syndrome may also reflect abnormalities in gonadotropin secretion. The apparent hyperplasia of Leydig's cells is considered only relative to their increased prominence as the area taken up by the seminiferous tubules shrinks.[12, 60] Histochemical studies of these cells reveal evidences of functional failure.[61] This is usually reflected in low-normal ketosteroid excretion and some clinical evidences of androgenic deficiency. It may, therefore, be inferred that some ICSH deficiency is common in this syndrome. The original hypothesis for the decreased ICSH secretion included both the lack of normal stimulation by the "X" hormone, and the inhibition of it by the androgen that is produced.[12]

Further evidence that FSH levels are elevated while ICSH is diminished in patients with Klinefelter's syndrome includes: (1) the stimulation of Leydig's cells by the ICSH effect of CGT,[62] (2) the inability to lower the gonadotropin levels with testosterone [52] which will decrease ICSH but not FSH,[63] and (3) the finding of a predominance of FSH in the urine of castrated humans.[64]

The gynecomastia frequently seen in Klinefelter's syndrome has been attributed to a number of possible hormonal imbalances.[12, 18, 23, 65, 66] Enlargement of mammary tissues occurs in hypogonadal states due to various testicular disorders,[9, 27, 65, 67] but is exceedingly rare in hypogonadism secondary to pituitary insufficiency.[6, 9, 68] Some degree of gynecomastia has been noted in all pubertal boys,[69, 70] and may be induced by the administration of CGT to normal adults [55] or to patients with Klinefelter's syndrome.[71] Thus it appears that pituitary gonadotropin, initially appearing during puberty and present in increased amounts in patients with testicular disease, is somehow causally related to the development of gynecomastia.

Summary

1. Thirty-one patients with hypogonadism, screened from 72,146 young men who entered the Air Force during a one-year period, were studied. This group represents only a fraction of the total number of such disturbances present in this population.

2. An intensive evaluation, including examination of buccal smears for the nuclear chromatin body, testicular biopsy, and measurement of hormonal

excretion, was performed upon each subject. Of the 31 patients, 20 were found to have Klinefelter's syndrome, and 17 of these were chromatin-positive.

3. A brief discussion of each type of hypogonadism is presented, using representative cases from the above series, and a detailed analysis of the present status of Klinefelter's syndrome is given.

4. An attempt is made to interpose recent advances in our knowledge into previously described pathophysiologic schemes of Klinefelter's syndrome. Emphasis is placed upon the possible role of excessive endogenous gonadotropin secretion in producing the typical testicular pathology and clinical features.

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SUMMARIO IN INTERLINGUA

Trenta-un juvene masculos con hypogonadismo esseva evalutate per examine physic, mesuration del excretion urinari de cetosteroides e gonadotropina, biopsia testicular, examine de frottis bucco-mucosal pro corpores de chromatina nuclear, e estimation objective del intelligentia. Duo in le gruppo habeva retardo del pubertate, un habeva panhypopituitarismo, duo habeva isolate deficientia de gonadotropina, e le resto habeva primari disordines testicular. Inter istes, quatro habeva acquirite defectos, duo habeva aplasia de cellulas germinal, tres habeva syndrome de Klinefelter con negativitate de chromatina, e 17 habeva syndrome de Klinefelter con positivitate de chromatina. Es presentate in detalio le constatationes clinic, hormonal, e bioptic, con le objectivo de fornir un guida in le diagnose differential del varie typos de hypogonadismo. Attention special es prestate a syndrome de Klinefelter con positivitate de chromatina a causa del frequentia de iste condition in le presente serie e a causa del currente interesse in iste forma de intersexualitate per aberration genetic.

Le variationes notate in le aspectos clinic e le pathologia testicular de iste syndrome es illustrate. Le diagnose pote esser facite con assecurantia per le constatation de positivitate de chromatina in un frottis ab un subjecto qui es phenotypicamente mascule, lo que exclude le rarissime casos de ver hermaphroditismo. Tamen, le diagnose de un patiente con negativitate de chromatina depende del constatation de hyalinisation tubular in association con defectos del spermatogenese e prominentia de cellulas de Leydig intra le tissu obtenite per biopsia del testes scrotal. Le separation de casos a negativitate de chromatina ab casos de aplasia del cellulas germinal es suggerite per le distincte conformationes pathologic e per le differentias in le incidentia de gynecomastia e eunuchoidismo in le duo gruppos.

Es interprendite le tentativa de evalutar le schema pathophysiologic originalmente presentate in le lumine del recente avantiamentos in nostre comprension del syndrome de Klinfelter. Le deficientia de cellulas germinal—causate per un anormalitate genetic in le gruppo a positivitate de chromatina—permitte un augmentate secretion de gonadotropina pituitari, primarimente de hormon folliculo-stimulante, lo que es presumitemente le effecto del absentia de un hormon de inhibition a origine in le cellulas spermatogene. Es presentate datos in supporto del conception que le elevate nivellos de gonadotropina induce le degeneration testicular e le gynecomastia. Un reducite secretion de hormon de stimulation interstitio-cellular es reguardate como responsabile pro le variabile hypofunction de cellulas de Leydig.

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CLINICAL STAFF CONFERENCE

CYSTIC FIBROSIS OF THE PANCREAS: CLINICAL STAFF CONFERENCE AT THE NATIONAL INSTITUTES OF HEALTH *

Moderator: PAUL A. DI SANT'AGNESE, M.D. *Discussants:* WILLIAM O. JONES, M.D., *Bethesda, Maryland;* and ZACHARIAS DISCHE, M.D., *New York, N. Y.*

DR. PAUL A. DI SANT'AGNESE: In recent years there has been an increasing interest in cystic fibrosis of the pancreas. It is now recognized that this generalized, inheritable disease which leads to dysfunction of all exocrine glands, mucus-producing and others, is one of the most common chronic diseases of childhood. In this country at the present time cystic fibrosis accounts for virtually all cases of pancreatic deficiency in the pediatric age group, for the majority of patients with chronic (nontuberculous) pulmonary disease, and presents a unique abnormality of sweat electrolytes, in that their concentration is markedly increased.[1] Although in the past the disorder was confined to the pediatric age group by its high mortality in infancy and early childhood, cystic fibrosis is now recognized with increasing frequency among adolescents and young adults. Among the most challenging of recent developments is the possible relation of fibrocystic disease to other chronic pulmonary and gastrointestinal disorders of adults.[2-4]

For many years the diagnosis was limited to patients with all of the manifestations of the syndrome, but it is now realized that gradation in, or absence of, involvement of organs or glandular systems usually affected is typical of this disorder and accounts for many variations in the clinical picture. Common to all patients with cystic fibrosis, regardless of the extent of the involvement of other systems, is an abnormally high electrolyte concentration in sweat. Therefore, the "sweat test" because of its simplicity and reliability is the cornerstone of the diagnosis in a disease marked by so many diverse clinical manifestations.

Cystic fibrosis of the pancreas has recently become one of the diseases under intensive investigation at the National Institute of Arthritis and Metabolic Diseases. Today we shall present two cases from our wards, one a child and one an adult, that illustrate some of the features of this common but still obscure disorder. We shall also describe some metabolic studies that lead to important genetic considerations and some chemical investigations that point to an altered mucopolysaccharide metabolism as the possible basic defect in cystic fibrosis.

The patients will be presented by Dr. William O. Jones.

DR. WILLIAM O. JONES: The first patient under discussion, T. O., is a three and one-half year old white female known to have cystic fibrosis of the pancreas.

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She was admitted to the Clinical Center on March 18, 1960, because of severe respiratory infection and malnutrition requiring prolonged hospitalization.

Case 1. Prior to this patient's birth a sibling had died at the age of four months of cystic fibrosis. Eight other siblings are living and well, and the family history was otherwise noncontributory. At the age of two weeks T. O. developed her first respiratory infection and began having frequent, loose, bulky, foul stools. Subsequent to this first episode there were frequent lower respiratory infections which required

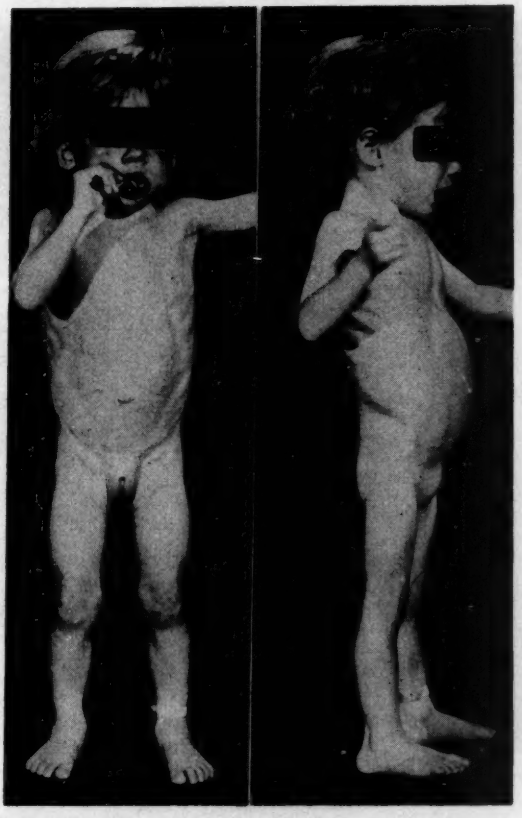

FIG. 1. T. O. at the age of 22 months (courtesy of Dr. Harry Shwachman).

and responded to antibiotic treatment. The weight gain of the child was poor. From the age of 11 months cough became continuous and malnutrition was marked. At the age of 16 months she was admitted to a hospital where the diagnosis of cystic fibrosis was confirmed on the basis of the physical, roentgenologic, and laboratory findings. The sweat test in particular was found to be abnormally high and there was no tryptic activity in the duodenal contents. Some improvement was noted following the institution of continuous oral antibiotic therapy and a low fat diet with added pancreatic extracts. Between the ages of 18 months and three and one-half

years this regimer was continued, but the patient failed to respond satisfactorily and hospitalization was needed on several occasions for treatment of respiratory infection. Various antibiotics were tried by mouth, by injection, and by inhalation with only temporary success.

On admission to the National Institute of Arthritis and Metabolic Diseases the patient was seen to be a poorly nourished, under-developed, chronically ill three and one-half year old girl with wasted buttocks, a distended abdomen, and an emphysematous chest (Figure 1). Weight was 9.5 Kg., or three standard deviations, and

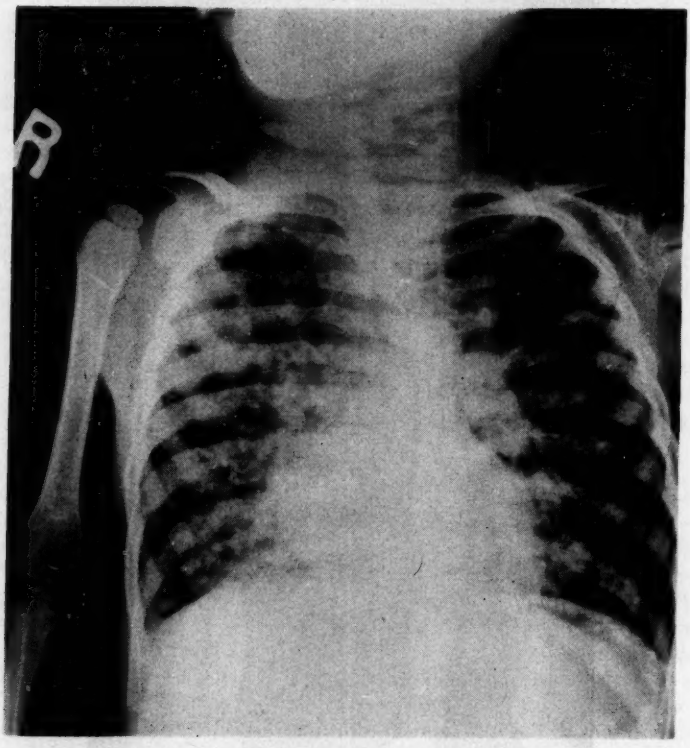

FIG. 2. T. O.: Roentgenogram of the chest on admission to the National Institutes of Health at age 3½ years.

height 32.5 inches, or four standard deviations, below the mean for her age. There was a frequent hacking cough productive of copious amounts of thick greenish sputum, moderate circumoral cyanosis, and marked clubbing of all fingers and toes. On percussion of the chest the note was markedly tympanitic, and on auscultation numerous râles were heard all over the pulmonary areas. On roentgenography signs of severe generalized obstructive emphysema were seen, as well as bronchopneumonic changes in both lungs (Figure 2). The sweat test was repeated and found to be abnormal and within the range characteristic for patients with cystic fibrosis. On culture of the nasopharynx *Staphylococcus aureus hemolyticus* (coagulase positive) and *Pseudo-*

monas aeruginosa were found on admission and on repeated examinations throughout the hospitalization.

The patient had been on chloramphenicol, erythromycin, and Albamycin orally prior to admission and this treatment was continued for the first week (Figure 3). Following reports of the sensitivities of the organisms isolated from nasopharyngeal and sputum cultures, a trial was initiated of intensive therapy with Chloromycetin and Terramycin by mouth, and penicillin and streptomycin by intramuscular injection and by inhalation. The response to treatment was not dramatic, however, and in view of the consistent finding of *Ps. aeruginosa* in cultures of the respiratory tract and of the sensitivity of this organism to Colymycin, this drug was started intramuscularly (3 mg./Kg. per 24 hours in divided doses). Terramycin and chloramphenicol (50 mg./Kg. of body weight per 24 hours in divided doses) were continued orally. During all of the hospitalization, inhalation therapy using a solution of 1% NaCl and 10% propylene glycol was given during naps and at night, all other supportive measures were used (e.g., physical therapy, postural drainage, etc.), and a low fat diet and pancreatic extracts were continued.

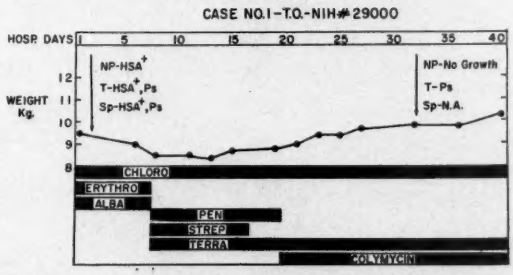

FIG. 3. Course, antibiotic therapy, and respiratory flora of T. O., age 3½ years. (Cultures: NP = nasopharyngeal; T = throat; Sp = sputum. Organisms: HSA^+ = *Staphylococcus aureus hemolyticus,* coagulase positive; Ps = *Pseudomonas aeruginosa;* N.A. = not available.)

As can be seen from the weight curve in Figure 3, there was marked improvement not only in nutrition, but in the respiratory status of the patient. Tachypnea and cyanosis disappeared, coughing was lessened, aeration of the chest was better, and only occasional râles could be heard. The roentgenograms also showed marked improvement and even the clubbing of the fingers became less marked. The patient's disposition changed accordingly and she became happier, more active, and playful. *Ps. aeruginosa,* however, could still be recovered from cultures of the throat.*

Case 2. The second patient to be presented, N. B., is a 27-year-old Negro female admitted to the Clinical Center on April 7, 1960, for evaluation of chronic pulmonary disease and possible bronchiectasis. The family history was noncontributory. The history was difficult to obtain in detail because of the patient's limited mental capacity.

N. B. was quite well during early childhood, with no respiratory symptoms and a good nutritional status. She had measles, chickenpox, and whooping cough without sequelae. At the age of 12 years she developed joint swelling of knees and

* The patient's response to sodium colistin methanesulfonate, provided by Warner-Lambert under the trade name Colymycin, was only temporary, and after seven weeks of sustained improvement extensive respiratory infection recurred. Thereafter, the course was progressively downhill and the patient died on June 15, 1960, of severe pneumonitis, despite treatment with sodium colistin methanesulfonate, chloramphenicol, erythromycin, Declomycin, and polymyxin.

wrists but was apparently only moderately incapacitated by this illness, which lasted for 12 months. During this period there was weight loss of several pounds and irregular fever. She remained well until the age of 15 years, at which time she developed an unexplained fever and despite the absence of joint symptoms was told that she had rheumatic fever. At this time she was also noted to have, apparently for the first time, corneal opacities of the right eye. Visual acuity on the right has decreased since then, although there has been no progression of symptoms.

At the age of 16 years the patient developed a persistent cough and fever and noted an increase in bowel movements from two to four per day. The stools were bulky, soft, light-colored, greasy, and foul-smelling. During the subsequent six years the productive cough, recurrent fever, and abnormal character of the stools persisted, requiring numerous hospitalizations for treatment. At the age of 22 years she was admitted to another hospital in this area for treatment and study for a period

FIG. 4. N. B., 27-year-old Negro female with cystic fibrosis of the pancreas.

of six months. A diagnosis of idiopathic bronchiectasis was made and the patient was discharged on antibiotic treatment. Among other conditions sarcoidosis was ruled out by extensive studies including two biopsies of lymph nodes. In the five years from the age of 22 to 27 years the cough, more severe at night, persisted. It was productive of from two to three tablespoonfuls of thick white mucus per day, which was frequently streaked with blood. Wheezing and dyspnea were made worse by respiratory infections, although the dyspnea was present even when climbing

stairs or during other physical exertion. Three years prior to admission, because of epigastric pain said to have been due to a peptic ulcer, the patient was placed on a low fat diet and abnormalities of the stools improved although they were still abnormal in character.

Physical examination on admission revealed a temperature of 37°C.; pulse 104; respiration 24; blood pressure 128/78 mm. Hg; weight 50.6 Kg.; height 64½ inches. The patient appeared to be a chronically-ill, thin, poorly-nourished, mentally-dull, 27-year-old Negro female (Figure 4). There was clubbing of the digital phalanges and minimal cyanosis of the nail beds. Examination of the eyes revealed corneal opacifi-

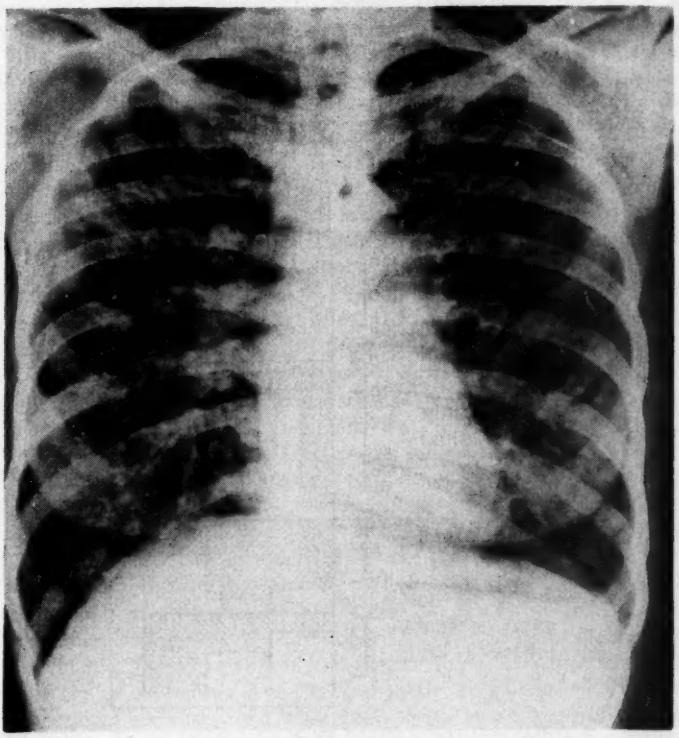

FIG. 5. Roentgenogram of the chest of N. B. on admission to the National Institutes of Health; age, 27 yrs.

cation of the right eye and diffuse tiny, dark opacities of the left lens. Examination of the chest revealed a symmetric rib cage with full and equal expansion. There was no detectable increase in the anteroposterior diameter of the chest. The percussion note was hyperresonant and coarse râles were audible over all pulmonary areas. The heart was normal. The remainder of the physical examination was unremarkable. Sputum culture revealed *Ps. aeruginosa, Staph. aureus hemolyticus* (coagulase positive), *Hemophilus hemolyticus,* and *Klebsiella.* A chest roentgenogram revealed diffuse nodular and streaking infiltrations in all lung areas (Figure 5), and the pulmonary artery segment above the cardiac silhouette was prominent.

Blood count and blood chemistries were within normal limits. On repeated examination the sweat electrolytes were abnormally elevated and within the usual range for patients with cystic fibrosis, with a range for sodium of from 76 to 108 mEq./L., and for chloride of from 107 to 119 mEq./L. During a period of seven days on dietary salt restriction (Na intake = 9 mEq./24 hrs.), and during a second metabolic period of the same duration in which restriction of sodium intake was maintained and 9-α-fluorohydrocortisone was administered daily, no significant change in sweat electrolyte concentration was observed (Figure 6). It will be noted that during dietary salt restriction there was very efficient conservation of sodium excretion by the kidneys, thus ruling out adrenal insufficiency. In metabolic studies (Figure 6) it was found that the patient had steatorrhea, with a total average fat content of 16 gm./24 hrs. (normal = less than 5 gm.) on a 100-gram fat intake (percentage fat absorption, 84%). A moderate degree of azotorrhea was also present. Duodenal drainage was attempted on two occasions but was unsuccessful both times. Extensive physiopathologic respiratory studies revealed definite evidence of obstructive bronchial disease. Because of the patient's cataracts the enzyme uridyltransferase was assayed in the blood and found to be normal.

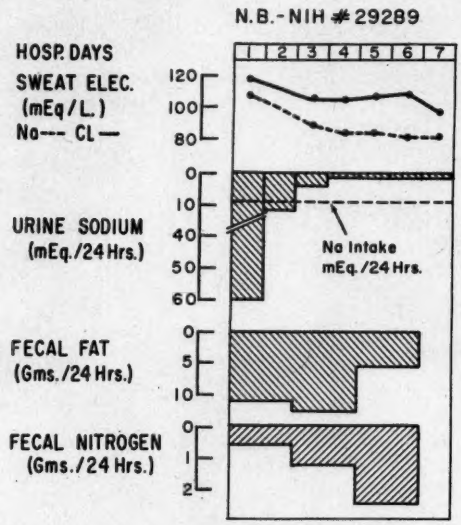

FIG. 6. Effect of dietary salt restriction on sweat electrolytes and on sodium secretion in urine. Fecal fat and nitrogen content (N. B., 27 yrs.).

The patient remained afebrile during the hospital stay but had a persistent loose cough, productive of small amounts of thick white sputum. She seemed excessively fatigued at all times. She improved after administration of Aureomycin orally, and a low fat diet supplemented with vitamins and pancreatic extracts. After a hospital stay of four weeks she was discharged on the above regimen to be followed in our outpatient department.

DR. PAUL A. DI SANT'AGNESE: The first case described by Dr. Jones, that of the three and one-half year old girl, is a good example of the classic picture of cystic fibrosis with all of the expected clinical and laboratory findings: onset of

symptoms shortly after birth, pancreatic achylia with its nutritional consequences, abnormally high sweat electrolytes, and chronic respiratory disease. In this patient, as in most others with this disorder, the pulmonary involvement dominates the clinical picture and usually determines the fate of the patient.

An interesting and somewhat unusual feature in this instance is the repeated isolation of *Ps. aeruginosa* in addition to *Staph. aureus hemolyticus* in cultures of the nasopharynx. The virtually constant finding of *Staph. aureus hemolyticus* as either the only or the predominant organism in the respiratory tract of patients with cystic fibrosis is well recognized.[1, 5] It has been demonstrated that in fibrocystic patients the invasion of the respiratory tract is not limited to any one bacteriophage type of staphylococcus,[6] and that resistance to infection by this organism is not decreased. Indeed, recent studies [7] show that in most patients with cystic fibrosis, levels of serum antibodies against staphylococcus are higher than in control individuals. The association between cystic fibrosis and *Staph. aureus* in the respiratory tract is so constant and so striking as to suggest that a metabolic abnormality in the pulmonary secretions of fibrocystics might be responsible for the consistent finding of this organism. Antibiotic therapy of the pulmonary involvement in patients with cystic fibrosis therefore has been aimed generally at controlling the pathogenic effects of this organism. When bacteria other than staphylococci are found in nasopharyngeal or sputum cultures the question always arises as to whether they play a role in the respiratory infection of cystic fibrosis or whether they are harmless symbiotic inhabitants of the respiratory tract in such patients, the way having been prepared for them by the staphylococcus, which then is destroyed by effective antibacterial agents.

Antibiotic therapy against staphylococcus had been ineffective in the patient under discussion and, therefore, treatment was initiated with Colymycin, a drug active against pseudomonas. The marked improvement in T. O.'s clinical condition that resulted (Figure 3) would certainly suggest that in this instance this organism played a pathogenic role in the respiratory infection. As no other case has been published, to my knowledge at this time, in which sodium colistin methanesulfonate has been used in cystic fibrosis, we must be cautious in interpreting these encouraging results until further experience is obtained.

The second patient presented by Dr. Jones, N. B., the 27-year-old Negro woman, is most unusual on several counts: her race, the fact that she survived to adulthood in relatively good condition, and that the onset of symptoms occurred only after the age of 14 years. The question might well be asked whether she has cystic fibrosis. However, the abnormally high sweat electrolyte concentration, the failure of sweat sodium and chloride levels to decrease following dietary salt restriction and steroid administration (Figure 6), the chronic digestive disturbances with abnormal, foul-smelling stools and steatorrhea, in combination with a chronic pulmonary disease characterized by bilateral bronchopneumonia and generalized obstructive emphysema firmly establish this diagnosis. In addition, other conditions which might have given rise to some of the symptoms had been ruled out, in particular sarcoidosis, by extensive biopsy and other studies. I cannot readily interpret the eye lesions and believe they are coincidental with rather than related to the basic condition. Galactosemia was briefly considered as a possibility but the assay for serum levels of uridyltransferase was normal.

The late onset of symptoms in this patient bears further comment. Cystic fibrosis is usually manifested at birth or in the first few weeks of life. However, we have on occasion seen a patient who has been, apparently, asymptomatic for months or even for the first three or four years of life, who eventually proceeds to develop all of the symptoms of the syndrome. In most instances such patients, as in the present case, had not been followed closely during the asymptomatic period and it is not known whether the abnormal sweat electrolyte concentration was present from the very beginning even without pancreatic and pulmonary manifestations. It is quite conceivable, however, that although in some cases all susceptible organs or glandular systems are affected, in others the extent of involvement may be too limited to give rise to clinical signs. Symptoms may then appear later, having been triggered by a change in some of the basic secretions in response to an altered physicochemical environment due to a temporary imbalance in the patient's homeostasis. This concept will be discussed more fully after Dr. Dische reports on some of the chemical studies of mucopolysaccharides.

QUESTION: Is there any evidence that cystic fibrosis is different in Negroes or in adults?

DR. PAUL A. DI SANT'AGNESE: It is well known that cystic fibrosis has striking racial predilections. Although its incidence is equally common in all branches of the white race and it is never reported in Mongolians, it is found rarely in Negroes. At Babies Hospital in New York, of more than 600 patients with this disease only four were Negroes, although the clinic population was about 30% Negro. In addition to being the oldest patient I have ever seen, this is the first adult Negro with cystic fibrosis of whom I have ever heard. Our experience shows that the picture of cystic fibrosis, when it occurs in nonwhites, is frequently incomplete and milder. This may well be due to a difference in the genetic endowment of the affected individual, a fact which may also be true of adult patients. The latter perhaps would not have survived to a fairly advanced age if they had not had a milder disease from the beginning.

This leads me to a consideration of the basic defect in cystic fibrosis and a discussion of some metabolic studies of the mechanisms of sweating in these patients which have a bearing on the problem.

The basic defect in cystic fibrosis is still unknown and speculation as to its nature has followed various channels. Deficiency in function of the autonomic nervous system, absence of an enzyme, or some other metabolic error have been proposed in general terms to explain the generalized dysfunction of exocrine glands.

Whatever the nature of the basic defect in cystic fibrosis, there is general agreement that it appears to be genetically transmitted, although there is no such consensus as to the mechanism of transmission. In various studies published in the past, before we knew of the abnormal sweat values and their genetic implications in this disease, Fanconi and Botztein, and Carter, Goodman, and Reed had concluded that a single recessive gene in the homozygous state caused the fully-manifested clinical picture. Also, several years ago Andersen and Hodges were of the opinion that an uncomplicated recessive trait dependent on a single gene was unlikely, although they did not offer any alternative explanation.

In more recent times and since the sweat test has afforded the means of

recognizing at least some of the heterozygotes, Childs has re-emphasized the autosomal recessive form of transmission in this disease, whereas recent investigations by Koch, Bohn, Lehman and associates in Germany in the last year have led them to the conclusion that the basic defect in cystic fibrosis is transmitted as an autosomal dominant character.

For the purposes of this discussion let us assume that the inherited character in fibrocystic disease is an autosomal recessive; it then follows that the patients who are homozygous for this gene are the ones who have all of the manifestations of the syndrome: chronic pulmonary disease, pancreatic achylia, and high sweat electrolytes.

This postulate also assumes the existence of heterozygotes among parents, siblings, and other relatives of known patients, and in some individuals of families in whom by chance no cases of cystic fibrosis have been recognized. If fibrocystic disease is transmitted as a recessive character and its incidence estimated at 1: 1000 live births, it then follows that about one in 20 of the population must carry the recessive gene. Actually, in various genetic studies the incidence of this gene in the population has been thought to be as high as 15 to 20%. This may seem like an excessively high figure to those of us not initiated in genetic lore. However, it has been shown repeatedly that natural populations are replete with deleterious recessive mutants concealed in the heterozygous condition by their normal alleles. As there is no evidence that heterozygotes have greater survival value or reproductive fitness than does the general population, it must also be assumed that there is a high mutation rate for the gene.

The question then is: Do these heterozygous individuals bear any stigmata of the disease? Indeed it has been recognized in the last few years that in many genetically transmitted pathologic conditions the heterozygotes have some manifestations of the trait. When it has been possible to pinpoint the deficient enzyme or the chemical abnormality responsible for the disease (as in galactosemia and sickle-cell anemia), it has been demonstrated that this same defect was present in the heterozygotes but to a lesser extent, and not sufficiently to give rise to symptoms.

So far no stigmata have been found in all individuals presumed to be heterozygous for the gene of cystic fibrosis. However, it was shown in our clinic some years ago that a significant proportion of asymptomatic relatives (both children and adults) of index cases show an elevation in sweat electrolytes similar to that found in patients with fibrocystic disease. Occasionally relatives of known patients also have some degree of chronic pulmonary involvement.

Some of these results are summarized in Figure 7 in which the levels of chloride in sweat from four groups of individuals are recorded, and in which 50 mEq./L. is taken as the dividing line between normal and abnormal concentrations. Several things will be noted: (1) none of the adult controls, 21 to 80 years of age, had sweat chloride levels above 50 mEq./L. and the great majority had much lower concentrations. With three exceptions none of these individuals was normal but suffered from a variety of conditions not related to cystic fibrosis. None had adrenal insufficiency, renal disease, or generalized obstructive emphysema, and none was related to a patient known to have cystic fibrosis; (2) seventeen per cent of parents and 29% of asymptomatic siblings of patients known to have cystic fibrosis had abnormally high sweat electrolytes; (3) most of the parents and siblings of index cases had higher chloride levels

in sweat than either adults or children who were controls, even when the values fell within normal limits; (4) conversely, in the parents and siblings of index cases with abnormally high values for chloride in sweat, the concentration was usually lower than in patients with full-manifested cystic fibrosis; (5) many individuals who must carry the recessive gene had concentrations of electrolytes in sweat which were well within normal limits; (6) when 24 adults (21 to 76 years old) with obstructive emphysema were tested it was found that 5 (20%) had elevated chloride and sodium in sweat. All other tests, including assay of duodenal enzymes, were negative in this group and there was no family history

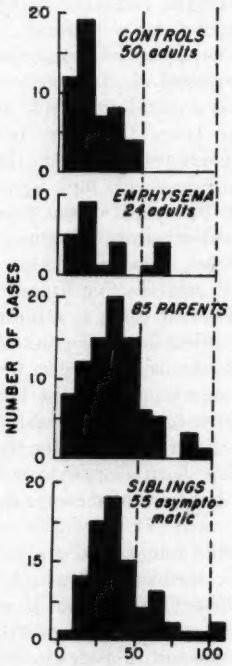

FIG. 7. Concentration of chloride in sweat from four groups as indicated. "Parents" and "siblings" are related to patients known to have cystic fibrosis.[8] (Reprinted with permission from *Pediatrics*, Vol. 24, No. 2, 1959.)

of cystic fibrosis.[19] Because up to the present time no other condition has been identified in which sweat electrolytes are increased (with the exception of untreated adrenal insufficiency), it was thought possible that such individuals might in reality have cystic fibrosis with only partial expression of the disease.

More important than these statistical results is the finding that response of sweat electrolyte levels to stress situations is affected by genetic endowment. It was shown some years ago by Conn [8] that in normal individuals there is a decrease in sodium and chloride content in response to various types of stress (e.g., dietary salt restriction, administration of steroids, environmental heat).

Indeed Conn felt that secretion of steroids leading to conservation of salt in sweat was the mechanism of acclimatization to hot weather. In patients with fully manifested cystic fibrosis (homozygotes according to the recessive hypothesis) the sweat defect consists not only of abnormally high electrolyte concentrations, but, more importantly from a physiologic standpoint, of the inability of sweat glands to respond normally to stress by decreasing the sodium chloride content of this secretion.

Some of these observations will become clearer from a study of Figure 6, which represents a balance study performed on the second patient reported (N. B., the 27-year-old Negro woman). Although it is the first time to my knowledge that such studies were performed in an adult with fully manifested cystic fibrosis, the results are quite in keeping with the many other similar investigations (largely unpublished) which we have carried out in the pediatric age-group. It will be noted that the levels of sodium and chloride in sweat did not decrease significantly when the patient was placed on dietary salt restriction for a period of seven days. However, the kidneys retained sodium and chloride under such circumstances in a very efficient manner, in keeping with our previous observations that renal and adrenal functions are normal in patients with cystic fibrosis. In a second metabolic period of seven days' duration, not recorded in this figure, exactly the same findings were obtained for both the sweat and the kidney responses when in addition to salt restriction steroids were administered.

It will be recalled that in the studies previously described (Figure 7) it was found that five of 24 adults with chronic pulmonary disease when tested were found to have abnormally high sweat electrolytes. At the time it was felt that in order to prove further whether or not these patients in reality had fibrocystic disease, the failure of the sweat electrolytes to decrease in response to stress should be demonstrated, since the lack of this normal response is so characteristic and unique to patients with this disorder. Accordingly (Table 1), three such patients were placed on dietary salt restriction (1 gm. of sodium per day) and simultaneously given desoxycorticosterone acetate (8 mg. per day) by intramuscular injection for a period of five days. At the end of the test period there was an unexpected drop in sweat electrolyte concentration to normal values. In one patient, R. R., sweat values sometime later were again abnormal.

At first we were quite puzzled by this response, but then it occurred to us that it was important to find out how parents of fibrocystic children (known heterozygotes for the cystic fibrosis gene) reacted under similar circumstances. As shown in Table 1, in two parents of index cases the high initial concentration of chloride and sodium in sweat decreased very markedly and to lower normal levels under the stimulation of salt restriction and the simultaneous oral administration of 9-α-fluorohydrocortisone for five days. Indeed, it is apparent from these figures that heat alone during the summer months may have induced a sufficient decrease in sweat electrolytes so that the high values obtained initially sometime before this study was undertaken had already decreased significantly in both subjects before the test period was started. Throughout the winter months both subjects again showed a spontaneous gradual rise to abnormal values for these two ions in the sweat.

These observations are only in the initial stages and must be pursued in a much larger number of cases. However, there does not seem to be much doubt

that so far as sweat electrolytes are concerned, (the only way in which we can compare the two groups at the present time), homozygotes and heterozygotes for the gene of cystic fibrosis behave in an entirely different physiologic manner to stress. Known and probable heterozygotes may present abnormally high levels of sweat electrolytes but the unknown fundamental defect responsible for this abnormality is not sufficiently great to interfere with their ability to conserve salt and decrease the concentration of sodium and chloride in sweat to normal levels after stress (e.g., salt restriction, administration of steroids, heat). On the other hand, patients with fully-manifested cystic fibrosis show little response to the same procedure and are not able to conserve salt in sweat under the same circumstances.

TABLE 1

Behavior of Sweat Electrolytes in Two Groups of Adult Individuals

	No. of Case	Name	Age and Sex	Date	Test*	Sweat mEq./L.	
						Cl	Na
Patients with chronic generalized emphysema	1	R. R.	38 yrs. F	1-10-57	Before test	75	84
				1-21-57	After test	23	25
				8-19-57	—	55	83
	2	M. F.	46 yrs. M	—	—	—	71
				—	Before test	72	77
				—	After test	32	29
	3	P. T.	52 yrs. M	2-24-56	—	71	73
				10- 4-56	Before test	55	65
				10-10-56	After test	32	16
Parents of patients with cystic fibrosis	4	W. A.	39 yrs. M	5-26-56	0	92	124
				5-11-57	Before test	43	59
				5-18-57	After test	18	35
				12- 8-58	0	41	65
				2-19-59	0	69	90
	5	A. H.	42 yrs. M	1-18-56	0	82	69
				10-19-58	Before test	36	20
				10-26-58	After test	19	21
				2- 1-59	0	46	59
				3-10-59	0	58	94

* Dietary salt restriction and simultaneous administration of DCA to cases 1, 2, and 3, and 9-α-fluorohydrocortisone to cases 4 and 5 for five days.

In conclusion, what is the significance of these observations? We can only speculate, but speculation is justified if it is recognized as an unproved hypothesis and thereby leads to further study. It is certainly possible that the unknown metabolic or enzymatic defect (perhaps concerned with the function of the central autonomic nervous system), which may be the common denominator of the generalized exocrine dysfunction in cystic fibrosis, may be absent in varying degree in homozygotes, heterozygotes, and possibly in intermediate cases according to their genetic endowment. This is true of other genetically transmitted errors of metabolism (e.g., sickle-cell anemia, galactosemia, and others). If a similar mechanism obtains in cystic fibrosis it may

account for some of the many variations in the degree of involvement and in the severity of the clinical picture.

This behavior of sweat electrolytes under stress must also be kept in mind in genetic family studies. It is probable, based on these data, that asymptomatic relatives of index cases who appear to have normal values for the sweat test at one time may have abnormal values under different circumstances. These findings do not invalidate the diagnostic value of the sweat test in homozygotes; however, normal results in heterozygotes must be interpreted with caution.

QUESTION: In recent times there has been a good deal of discussion as to the possible relation of cystic fibrosis of the pancreas to asthma and to some of the common gastrointestinal and pulmonary disorders of adults. Would you comment on these two aspects?

DR. PAUL A. DI SANT'AGNESE: We have already mentioned the occurrence of a high sweat test in a proportion of adults with generalized obstructive emphysema and mentioned their possible relation to cystic fibrosis. Our findings in this group of patients have been confirmed by others, notably Bohn, Koch and associates [3, 4] in Germany. These investigators in very elaborate studies have pointed out that peptic ulcer is very common in families thought to have patients with cystic fibrosis and ventured the opinion that the latter disorder may turn out to be even more frequent in adults than in children, although somewhat different in its consequences and clinical manifestations. The association between peptic ulcer and chronic pulmonary disease is well-known and has been recognized for some time. However, the main resemblance of the adult patients studied by the German investigators to the children with cystic fibrosis is in the fact that the sweat electrolyte levels are abnormally elevated. Many of the other features of the syndrome of cystic fibrosis are absent. Further study is therefore needed before this subject can be clarified further. Without question, however, the possible relation of fibrocystic disease in children to some of the more common pulmonary and gastrointestinal disorders of adults is one of the most challenging of the recent developments in this field.

In recent times it has been stated that patients with various types of allergy, and those with bronchial asthma in particular, have higher sweat electrolytes than do normal children or pediatric patients with other conditions. These investigations have not been extended to adults. Hsia [10] is the foremost proponent of this thesis. More recently Van Metre et al.[11] and Kulczycki and Shwachman [12] have taken up this subject and find that the sweat electrolytes of children with asthma are normal unless they have both allergy and cystic fibrosis. The combination of the two conditions occurred in 16% of fibrocystics in the latter series [12] and was felt by the authors not to exceed the expected frequency in the general population and to be due to coincidence alone.

We charted the sweat chloride values of 50 children discharged from the Babies Hospital in New York with a final diagnosis of bronchial asthma and compared these figures with the levels for sweat chloride of patients with cystic fibrosis and for controls observed during the same period. The distribution of values for sweat chloride is precisely what would be expected in any biologic measurement, with known fibrocystics tapering down to the 50 mEq./L. line, patients with asthma decreasing as they near this limit, and with two individuals showing values of slightly more than 50 mEq./L. When the figures for chlorides for all the asthmatics were summed, averaged, and compared with those

of a large number of controls seen during the same period of time, there was a difference of only 4 mEq./L. between the means for sweat chloride values for asthmatics and for controls. The difference is not of statistical significance (standard error of means = 1.78).

It would seem at least possible in view of the distribution of sweat electrolyte levels that at times patients who in reality have cystic fibrosis are included among the children discharged as having asthma. The resemblance of the two conditions on physical and roentgenographic examination is indeed well known. If this were true one would have to include only one or two individuals with an erroneous diagnosis among the asthmatics to get mean values for sweat NaCl farther apart in the groups under consideration and alter their statistical significance. In conclusion, the present evidence is that patients with true bronchial asthma have normal sweat electrolyte values, but that there are individuals with borderline values who in reality may have cystic fibrosis in a partially manifested, unrecognized form.

We shall now describe some of the investigations of the chemical structure and physicochemical behavior of mucopolysaccharides in cystic fibrosis. We are indeed fortunate in having Dr. Zacharias Dische, Professor of Biochemistry at Columbia University, here today from New York to discuss this subject.

DR. ZACHARIAS DISCHE: I shall describe briefly some chemical investigations of mucus in cystic fibrosis which were conducted at Columbia University in our laboratory in conjunction with Dr. di Sant'Agnese's project at Babies Hospital in New York, and which are now being pursued as a joint project by our department at the College of Physicians and Surgeons in New York and here at the National Institute of Arthritis and Metabolic Diseases.

It has been known for several years that human mucus contains complexes between carbohydrates and proteins (so-called mucopolysaccharides) that account for most of the highly polymerized organic constituents of mucus itself. Investigations, first carried out on mid-term human cervical mucus which can be obtained in very pure form, showed that the carbohydrate in these complexes is a fuco-mucopolysaccharide consisting of hexose, hexosamine, and a large proportion of fucose. Werner in Sweden later demonstrated that there is in this type of mucus a fourth and very important constituent, sialic acid.

It seemed possible that changes in the chemical structure and in the physicochemical behavior of these compounds might explain some of the abnormal characteristics of mucous secretions in cystic fibrosis (e.g., increased viscosity), which may give rise to many of the symptoms observed in this disease. In selecting body secretions of fibrocystic patients for study it appeared that the most fruitful initial approach would be to investigate mucopolysaccharides of the duodenal contents of such subjects. The bronchial mucus in this disorder, which comes to mind immediately because of the symptoms its accumulation gives rise to, did not appear to be suitable for chemical analysis because it is generally contaminated by secondary infection and is subject to marked evaporation. On the other hand, mucus from duodenal contents was available in almost sterile form and was easily obtainable by duodenal drainage in sufficient quantities for detailed chemical analysis. It was realized, of course, that mucus in duodenal juice is derived from bile, Brunner's gland secretion, and from the pancreas (the latter is missing in fibrocystics with pancreatic achylia). However, presumably any chemical change in mucus structure is equally present

in secretions throughout the body produced by many different glands in the generalized disorder, cystic fibrosis. As no analysis of this nature had been carried out in control individuals, it was also necessary to study such subjects for purposes of comparison.

The first serious difficulty, and one immediately encountered, was the presence of bile pigments in duodenal fluid, which interfered with colorimetric methods for detailed analysis of the carbohydrate components of mucus. This problem was solved after considerable experimentation by treating duodenal contents with a 1:1 mixture of benzene and ethanol, which precipitated all of the carbohydrate containing material and yet kept the bile pigments in solution.[13] The next step was to redissolve in water the material precipitated by the benzene-ethanol mixture and then remove the compounds containing mainly protein by adding trichloroacetic acid (TCA). The material thus obtained and soluble in TCA was then fractionated according to its solubility in ethanol at various concentrations.[14, 15] Two fractions which were first separated were precipitable by ethanol—at 50% (fraction A), and at 67% (fraction B). The supernatant was then concentrated and a fraction precipitated with 90% ethanol (fraction C). The fraction soluble in 90% ethanol (fraction D) was obtained by removing the latter and dialyzing the solution.

Analysis of the carbohydrate components of these fractions was then performed on samples of duodenal contents obtained from both patients with cystic fibrosis and controls of the same age group. Six sugars or sugar derivatives were found to be present in significant quantities: galactose, mannose, fucose, glucosamine, galactosamine, and sialic acid. No significant amount of glucose could be demonstrated by paper chromatography.

It was also found that these constituents formed two different types of mucopolysaccharide which had in common galactose, fucose, glucosamine, and sialic acid. However, the fractions less soluble in alcohol (A and B) also contain galactosamine in their molecule. On the other hand the fractions which are more soluble in alcohol (C and D) contain mannose and probably no galactosamine.

The four fractions described and their component sugars were present in samples both from patients with cystic fibrosis and from controls, and there was no difference in the *qualitative* analysis of mucopolysaccharides in duodenal contents between these two groups of subjects. Mention should be made at this stage of the work of Bauer[16] in Switzerland, who confirmed most of these results, but who drew the completely unwarranted conclusion that there are no chemical differences in duodenal fluid mucopolysaccharides between those persons with fibrocystic disease and controls. This erroneous conclusion was prompted by the failure to follow up these qualitative experiments with a quantitative evaluation of the distribution of these compounds in various fractions, which is where are found most of the significant variations that separate fibrocystics from controls.

Very significant differences between patients with cystic fibrosis and controls were found in the *quantitative* analysis of the different fractions separated by their solubility in ethanol and in the physicochemical behavior of the precipitate obtained with the ethanol-benzene mixture. First, when duodenal fluid is precipitated with the latter solution a great part of the mucopolysaccharides in samples from fibrocystic patients becomes insoluble in water and is apparently

irreversibly denatured. Whereas this sequence obtains in almost all samples from patients with cystic fibrosis (regardless of whether pancreatic function is affected), it does not obtain in any of the samples from controls. Second, in some of the fractions there are differences between the fibrocystic patients and controls so far as the ratios of certain constituents are concerned. This is apparent from Figures 8 and 9 where the ratios of fucose to sialic acid and of fucose to hexose are compared. As can be seen, the ratio of fucose to sialic acid becomes smaller as the solubility of the fraction increases. The less soluble fraction, which is precipitable with 50% ethanol, has by far the highest ratio.

The mucopolysaccharide fraction which becomes insoluble in water after the benzene-ethanol precipitation and is found only in pediatric patients with cystic fibrosis is also characterized by a low sialic acid, high fucose content (Figure 8). In fact, the content of sialic acid of this fraction is similar to that

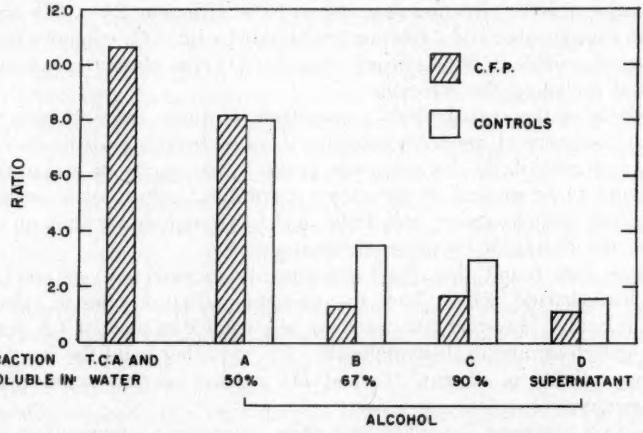

FIG. 8. Molar ratios of fucose to sialic acid in mucoprotein fractions of duodenal juice from pediatric patients with cystic fibrosis of the pancreas (C.F.P.) and from controls.

of fraction A precipitated with 50% ethanol from duodenal fluid of patients with cystic fibrosis. Its fucose to hexose ratio (Figure 9) is significantly higher than that of any other fraction both in controls and in patients under study. This fraction, which is characteristic of fibrocystics, constitutes approximately 50% of the total mucopolysaccharide content of the duodenal fluid in such patients. It can be expected that since sialic acid is the only hydrophilic component in the carbohydrate part of the mucopolysaccharides, the solubility would be increased by its presence in the molecule. The fucose instead is present as an end group, on which the carbon-6 atom projects out in a perpendicular direction from the main chain of the sugars, and has a hydrophobic methyl group on the surface which will tend to decrease the solubility. It is probable, therefore, that the reactivity of these mucopolysaccharides is significantly changed in patients with cystic fibrosis because a large part of these compounds is liable to denaturation and loss of solubility. This would point to the possi-

bility of a disorder either in the metabolism of sialic acid or in the processes leading to incorporation of sialic acid into the mucopolysaccharide molecules.

These results gave us some leads which are now being investigated. First, if there is a general disorder in sialic acid metabolism, this may be reflected in the composition of the mucopolysaccharides in urine. We found in our laboratory two years ago that the urine in normal adult individuals and adult patients with conditions other than fibrocystic disease contains eight different mucopolysaccharide fractions. These were separated by continuous-flow electrophoresis, using a technic which we developed. The fractions exhibited a very characteristic behavior; there was, for example, an inverse correlation between the sialic acid and the fucose content of their individual components.[17] It seems probable that these compounds in the urine reflect metabolic processes of mucopolysaccharides in the body. It appeared, therefore, of interest to see whether in urine from patients with cystic fibrosis there are characteristic changes in

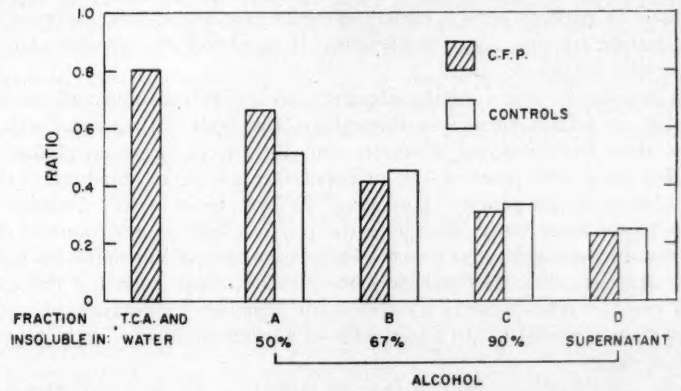

FIG. 9. Molar ratios of fucose to hexose in mucoprotein fractions of duodenal juice from pediatric patients with cystic fibrosis of the pancreas (C.F.P.) and from controls.

the composition or distribution of this type of compound. This investigation is now under way at the National Institute of Arthritis and Metabolic Diseases in conjunction with our laboratory at Columbia University.

Study of a second problem was started in conjunction with Dr. L. J. Cizek and Dr. S. Chien of the Department of Physiology at our college at the suggestion and initiative of Dr. J. Charles Pallavicini, when he was still in our department and before he moved to the National Institute of Arthritis and Metabolic Diseases. Under certain circumstances, and especially in hot weather, there is a massive loss of sodium chloride in the sweat of patients with cystic fibrosis, leading to salt depletion. It appeared, therefore, of interest to investigate the effect of desalting of the organism on the chemical structure and physicochemical properties of mucus. Dogs were salt-depleted by injecting a hypertonic solution of glucose into the peritoneal cavity. One day later saliva was obtained directly from the submaxillary gland following a surgical procedure which permitted stimulation of the chorda tympani by electric current, or by administering drugs which stimulated the parasympathetic nerves. The saliva was then

fractionated with ethanol in a similar way to the duodenal fluid and the mucopolysaccharides in the various samples obtained were analyzed. After exhaustion of the submaxillary gland by maximal stimulation, there appeared in the less soluble fraction a much higher amount of mucopolysaccharides, which were easily denatured and rendered insoluble in water. These findings are somewhat analogous to the phenomena which take place in the duodenal fluid of the fibrocystics. These experiments remain under investigation and we hope to clarify further the mechanisms involved.

DR. PAUL A. DI SANT'AGNESE: Of a large number of subjects tested, the insoluble mucopolysaccharide fraction which Dr. Dische described was found in the duodenal contents of almost all patients with cystic fibrosis and pancreatic achylia, and in a majority of those with normal or reduced pancreatic function. This mucopolysaccharide fraction is, therefore, presumably independent of the presence or absence of pancreatic juice and is apparently not affected by tryptic activity, a fact borne out also by in vitro experiments. In well over 100 normal individuals or patients with a variety of other conditions, this abnormal mucopolysaccharide fraction was not present. It is, therefore, peculiar and unique to fibrocystic patients.

If it is assumed that a similar abnormal composition of mucopolysaccharides is present in mucus secretions throughout the body in patients with cystic fibrosis, then the decreased solubility and the increased susceptibility to denaturation of a large part of the mucopolysaccharides in duodenal fluid may give a clue as to the genesis of many of the symptoms of this disorder. It is possible to speculate that a change in the physicochemical environment of these mucus secretions might cause irreversible precipitation of mucoproteins in organs such as the pancreas, the liver, and the bronchi, thus initiating the chain of clinical events. The presence of this easily denatured substance, according to this hypothesis, would be the forerunner of further difficulties and not a consequence of them.

From what has been said, it is clear that there are in cystic fibrosis three defects in exocrine secretions which need further study: (1) an electrolyte abnormality of sweat, saliva, and tears; (2) a change in the chemical structure and physicochemical behavior of mucus secretions in duodenal fluid and, probably, throughout the body; (3) an increase in parotid secretory rate. The common denominator responsible for the widespread dysfunction of so many and perhaps all exocrine glands and, therefore, the pathogenesis of cystic fibrosis, has thus far escaped detection. It is generally agreed that the basic defect in this disorder, whatever its nature, is genetically transmitted. From the studies of the behavior of sweat electrolytes previously described, there is suggestive evidence that this unknown basic metabolic or enzymatic defect (perhaps concerned with the function of the autonomic nervous system) may be absent in varying degrees according to genetic endowment. This would then affect the expression of the generalized disorder—cystic fibrosis of the pancreas—and condition the variety and severity of the clinical manifestations in different individuals.

QUESTION: Is there a disturbance analogous to cystic fibrosis known to occur spontaneously in any animal species, and if not, is it possible to reproduce a similar picture in any way?

DR. PAUL A. DI SANT'AGNESE: I am not aware of any disease of animals which resembles cystic fibrosis. Several years ago Farber in Boston reported that by repeated injections of pilocarpine into newborn kittens he was able to reproduce in the pancreas a pathologic picture similar to that of cystic fibrosis. These experiments have not been followed, to the best of my knowledge.

QUESTION: How common is the involvement of the liver in cystic fibrosis, and what is the histogenesis of the cirrhosis in this disorder?

DR. PAUL A. DI SANT'AGNESE: The initial lesions of focal biliary cirrhosis are present in a great majority of patients at autopsy. There is plugging of the bile canaliculi by abnormal secretions surrounded by an area of fibrosis and neo-production of biliary ductules. These anatomic changes have been seen as early as three days of age. At times the process becomes more diffuse and gives rise to a distinctive type of cirrhosis, which we have called by the purely descriptive name of "multilobular biliary cirrhosis with concretions." As this is a focal disturbance and there are large areas of hepatic parenchyma functioning normally, the so-called liver function tests are frequently normal and jaundice is absent or very slight. After years of alternating destruction and regeneration, the architecture of the liver is altered and venous return through this organ is impaired. It is only with the appearance of portal hypertension and its manifestations (hypersplenism, ascites, gastrointestinal bleeding) that the cirrhosis becomes symptomatic.

SUMMARIO IN INTERLINGUA

Es presentate duo patientes con fibrosis cystic del pancreas. Le prime, un puera de duo annos e medie de etate, presentava omne le characteristicas del morbo e habeva un sever affection chronic del pulmon. *Pseudomonas aeruginosa* esseva culturate repetitemente ab le nasopharynge e le sputo, e le patiente respondeva al tractamento con methanesulfonato de colistina a natrium (Colymycina). Le secunde patiente, un feminina negre de 27 annos de etate, experientiava un tardive declaration del symptomas sed presentava omne le manifestationes de fibrosis cystic. Iste secunde patiente representa un inusualissime caso de iste disordine. Illa es le prime de su etate e de su racia unquam reportate con morbo fibrocystic.

Le defecto basic in fibrosis cystic es discutite. Es describite studios metabolic del mechanismo de sudoration in patientes con iste disordine. In le curso del hic-reportate investigationes, il deveniva clar que il occurre varie responsas a stress in le electrolytos del sudor in dependentia del dotage genetic. Es proponite, per consequente, le these que le defecto metabolic fundamental in fibrosis cystic pote esser presente in differente grados in homozygoticos, heterozygoticos, e casos intermediari e que isto explica possibilemente multes del variationes in le tableau clinic e in le severitate del morbo mesme.

Es discutite brevemente le relation inter fibrosis cystic in juveniles e le occurrentia de iste morbo in adultos si ben como su correlation con asthma bronchial.

Es describite investigationes de anormalitates del structura e del physico-chimismo de mucopolysaccharidos in le contento duodenal de patientes con fibrosis cystic del pancreas. Alterationes structural del mucopolysaccharidos que occurre in iste morbo ha le effecto de un reduction de lor solubilitate. Es proponite le these que—si simile anormalitates compositional del secernite muco es presente in omne partes del corpore de patientes con fibrosis cystic—le reducite solubilitate del mucopolysaccharidos in le liquido duodenal e le augmentate susceptibilitate de un grande parte de ille mucopolysaccharidos de esser disnaturate pote, indirectemente, offerer indicios con respecto

al genese de multes del symptomas de iste disordine, proque le reducite solubilitate e le concomitante disnaturation mucopolysaccharidic va resultar in obstruction in multe organos del corpore e assi in le initiation de un catena de evenimentos clinic.

Es delineate brevemente le tres defectos del secretion exocrin presente in fibrosis cystic le quales require investigationes additional.

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CASE REPORTS

RECURRENT MENINGITIS ASSOCIATED WITH CONGENITAL DERMAL SINUS*

By Dolores Méndez-Cashion, M.D., *San Juan, Puerto Rico,* and Ricardo Cordero, M.D., *Santurce, Puerto Rico*

Congenital dermal sinuses are depressions or tracts lined with stratified squamous epithelium which apparently result from defective separation of the neuroectoderm from the epithelial ectoderm along the mid-dorsal aspect of the embryo. In 1926 Moise [1] related these lesions to intracranial infection when he reported a case of staphylococcal meningitis in which the portal of entry was a congenital dermal sinus in the sacral region. His patient, an 18-year-old male, recovered after lumbar laminectomy with drainage. Several reports followed of meningitis secondary to similar lesions along the spinal axis.[2-4]

In 1949 Mount [4] reported two cases of sinuses in the occipital area expanding into posterior fossa dermoids. In 1951 Cardell and Laurance [5] collected from the literature 34 cases of congenital dermal sinuses in various locations and added one of their own. Of these, 23 were infected. Their own patient succumbed to fulminating penicillin-resistant staphylococcal meningitis.

Ingraham and Matson [6] reported 10 patients treated surgically for intracranial dermal sinuses. Results were poor in the infected group. They pointed out that surgical treatment before development of intracranial infection is relatively simple and should be rewarded by complete cure. However, since congenital dermal sinuses are rather rare, and their clinical manifestations prior to the onset of complications appear to be deceptively benign, most cases are diagnosed after infection has ensued.

Two cases of congenital dermal sinus of the occipital region and one of the lumbosacral area have been treated at the San Juan City Hospital since 1950. We will report the last patient in detail. We will review also such clinical features of the condition as may lead to early recognition and optimal management.

Case Report

A five-year-old male was admitted for the second time to San Juan City Hospital on June 19, 1959, because of frontal headache, low grade fever, and vomiting of five

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From the Department of Pediatrics and the Section of Neurology and Neurological Surgery of the University of Puerto Rico School of Medicine and the San Juan City Hospital.

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FIG. 1. Small fistulous opening of congenital dermal sinus.

days' duration. Past history and review of the record revealed that the patient's first admission had been from January 1 to January 20, 1959, because of acute meningitis, with fluid of purulent characteristics but without growth on culture.

On physical examination the patient appeared to be well developed, well nourished, and acutely but not critically ill. Temperature, 100.2° F.; pulse, 120; respiration, 28. Spinal puncture revealed cloudy fluid with a white cell count of 3,682/cu. mm. of which 78% were polymorphonuclears; sugar, 44.6 mg./100 ml.; total protein, 93.6 mg./100 ml. Smears were negative; cultures subsequently showed no growth. Because of recurrent meningitis the patient's scalp was shaved, and a very small, doubtful fistulous opening was found over the occiput in the midline (Figure 1). There was slight palpable thickening of the skin around the dimple. Skull x-rays were taken and reported to be negative. Cone views focused over the skin lesion

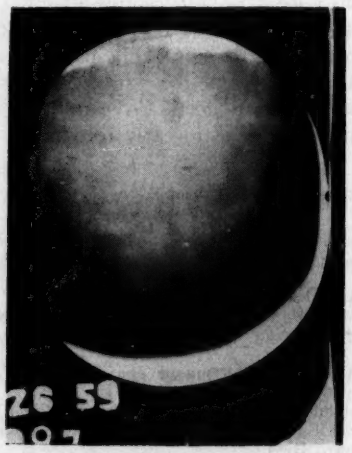

FIG. 2. Midline occipital skull defect.

were then ordered; they revealed a defect in the midline occiput measuring about 1 cm. in diameter, with sclerotic borders (Figure 2). The patient was treated with a combination of penicillin, sulfadiazine, and Chloromycetin, and responded well. He was discharged on July 3, 1959, for readmission.

The patient was readmitted on July 10, 1959, for neurosurgery. On further questioning at this time the mother stated that when the patient was a baby she had noticed a small scalp lesion, which was forgotten as it became covered with hair. Surgery was performed on July 13, 1959, by one of us (R. C.). The findings at operation are shown in Figure 3, and diagrammatically in Figure 4. The sinus tract

FIG. 3. Operative findings (see text).

started at the skin and crossed the dura beneath the confluence of the longitudinal and transverse sinuses, under the tentorium cerebelli. It expanded into a cyst, 4 cm. in diameter, which was located between and adherent to the cerebellar hemispheres, and ended on the floor of the fourth ventricle. There was no obstruction to the flow of the cerebrospinal fluid. On section the sac was shown to be filled by a grayish white caseous material containing hairs, and was diagnosed pathologically as a dermoid cyst. Figure 5 shows the operative specimen.

The postoperative course was marked by fever and nuchal pain, with meningeal reaction. Spinal fluid examination on July 18, 1959, showed 920 white cells/cu. mm. 53% of which were polymorphonuclears; sugar, 36 mg./100 ml.; protein, 126.0 mg./100 ml. No organisms were shown on smear or culture, but the patient received full antibiotic therapy. He was discharged asymptomatic on July 28, 1959. On follow-up, physical and neurologic examination was negative. The patient has remained well and is attending school.

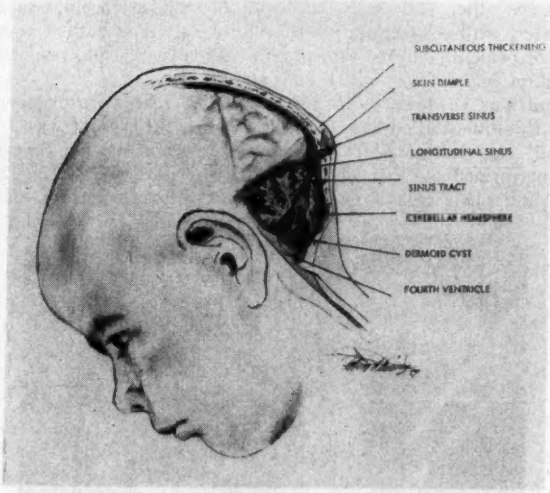

FIG. 4. Occipital congenital dermal sinus leading to dermoid cyst within the fourth ventricle.

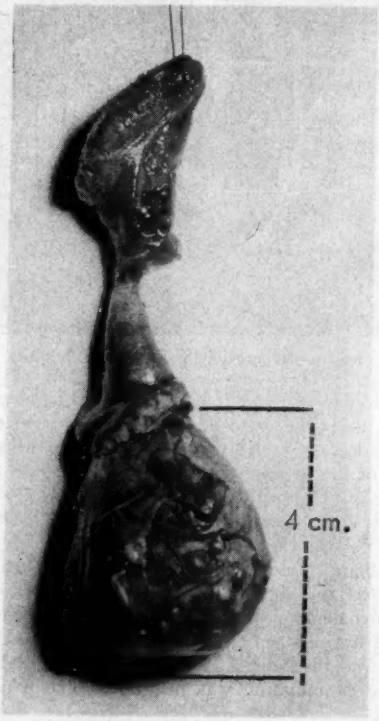

FIG. 5. Operative specimen.

Discussion

Very early in embryonic life the neural groove appears on the dorsal aspect of the embryo, later becoming invaginated to form the neural tube. At about the end of the fourth week after conception the neural tube becomes separated from the epithelial ectoderm. Anomalous separation at this stage is believed to produce congenital dermal sinuses.[3] The epithelial defect may be no more than a cutaneous dimple; if deeper, it may constitute a pilonidal sinus, but if associated with failure of development of the mesodermal structures, it may extend all the way into the spinal canal or cranial cavity.

The sinus may expand into a cyst at any point, most often at its distal end, and also just beneath the skin. This cyst is called an epidermoid when it is lined with stratified squamous epithelium and contains only epithelial debris, but it is a dermoid when it contains sebaceous material and hair, and when the lining includes elements from the deeper layers of the skin. It is also developmentally possible for a dermoid to exist alone, without a sinus, or with an incomplete one. The symptoms are then those of an intracranial or intraspinal mass.

The developmental arrest may occur anywhere in the midline. It is, however, most frequent at the occiput and in the lumbosacral region. It has been reported also on the dorsum of the nose.[7]

Signs and symptoms may be divided into four groups. First the external signs appear, which may be so innocent that in most cases the diagnosis is not made until complications ensue. Thus, a careful search with a good light and shaving of the hair may be necessary. The most constant external manifestation is a small dimple or sinus opening at or near the midline. Hairs may protrude from this opening, or normal hair may be absent over a small area around the lesion. Small hemangiomas or port-wine stains are frequent. The skin beneath the dimple may be thickened, or there may be an actual subcutaneous mass, a mild inflammatory reaction, or drainage of fluid, sebum, or pus.

Roentgenograms usually reveal a midline defect in the vicinity of the external lesion. Rarely, the sinus tract may be so narrow that it traverses the suture without a radiographic defect, although one is demonstrable at operation. Separation of the sutures may be seen when increased intracranial pressure exists.

Symptoms due to the presence of an intracranial or intraspinal mass will be those of hydrocephalus if it is causing obstruction. The intracranial mass itself will produce symptoms of increased intracranial pressure, but it may remain silent until it becomes expanded by sebum or inflammatory exudate. Intraspinal masses may become manifest by disturbances of locomotion, urinary complaints, and other neurologic abnormalities, and in children presenting with such complaints this diagnostic possibility should be kept in mind.

Finally, an existing connection with the meninges, or destruction of the cyst wall by infection, may result in meningitis or abscess. Osteomyelitis has also been reported.[6] Infection is most often staphylococcal or of unknown etiology, and in low-lying lesions may be due to *Escherichia coli.*

It is quite clear that midline occipital dimples and sinuses, and those high over the spinal axis, should be excised, particularly when x-rays demonstrate a defect in the bone, or when there is any indication of increased intracranial

pressure. Excision of a dermal sinus in the scalp should include preparation to carry out intracranial exploration should it be found necessary.

A careful search for the lesion is indicated in every case of unexplained meningitis, and in those due to staphylococci, or those with negative bacteriology. Recurrent meningitis suggests an external connection with the central nervous system, congenital or traumatic, or a defect in immunologic response.

There is less agreement on the management of low lesions in children with no symptoms. At times this may pose a problem of judgment for the physician. Dimples over the lumbosacral region and pilonidal sinuses are very frequent, and most of them do not extend beyond the fascia. About 25% of all children show some minor defect of a vertebral spine or lamina on roentgen examination.[8]

Lanman [9] has commented that "the use of prophylactic surgery (in pilonidal sinuses) can easily be carried to ridiculous extremes. . . ." Haworth and Zachary [10] believe that if a sinus is found in any position over the spine, and pressure on the adjacent skin does not expose the base, it should be excised with its tract, since it is impossible by external examination to distinguish sinuses that communicate with the central nervous system from those that do not, as even though sinuses over the coccyx do not often communicate, infection may still find its way to the extradural space.

The association of a skin dimple with a bony defect suggests that there may be extension of the cutaneous lesion into the spinal canal. Matson [11] thinks that prophylactic major surgery should be performed for sinus tracts at any point along the spinal axis when associated with an underlying bony defect revealed by x-ray.

Summary and Conclusions

1. A case of occipital congenital dermal sinus complicated by recurrent meningitis has been presented.

2. The signs and symptoms of the condition have been reviewed.

3. Congenital dermal sinuses should be looked for carefully in asymptomatic children as well as in cases of unexplained meningitis, particularly if due to staphylococci or of unknown etiology.

4. The optimal time for excision of high lesions is before complications occur, and surgery should include preparations to enter the cranial vault if necessary.

5. Patients with pilonidal sinuses require individual evaluation. X-ray studies should be performed, and the possibility of a connection with the central nervous system should be kept in mind.

Summario in Interlingua

Congenite sinos dermal es depressiones o tractos revestite interiormente de stratificate epithelio squamose. Apparentemente illos resulta de un defective separation del neuroectoderma ab le ectoderma epithelial al longo del aspecto meso-dorsal del embryo. Le sinus individual pote expander se ad in un cyste a non importa qual puncto. Isto occurre le plus frequentemente al termino distal del sinus o justo infra le pelle. Quando illo es extendite completemente usque ad in le cavitate cranial o ad in le canal spinal o si le parietes del cyste es erosionate per infection, illo pote servir de porta de entrata pro infective agentes. A su termino distal le cyste pote causar symptomas de un massa intracranial o intraspinal.

Le apparentia externe es usualmente deceptivemente benigne. Le presentia del sinus debe esser suspicite e cercate meticulosemente, preferibilemente ante le occurrentia de un infection e particularmente in casos de non explicate meningitis, super toto si illo es causate per staphylococcos o si su etiologia es occulte. Le sinus pote occurrer non importa ubi al longo del linea medial, sed illo se trova le plus frequentemente in le regiones occipital e lumbosacral. Su presentia ha etiam essite reportate al dorso del naso. Capillos protrude a vices ab le apertura, sed il etiam occurre que le capillatura normal es absente in un micre area circum illo. Micre hemangiomas o nevos vascular es frequente. Leve formas de reaction inflammatori, spissification del pelle, o un massa subcutanee es etiam possibile. Occasionalmente il ha drainage de liquido, de materia sebacee, o de pus. Usualmente le roentgenogramma revela un defecto ossee mesolineal in le vicinitate.

Le autores reporta le caso de un puero de cinque annos de etate in qui le correcte diagnose esseva establite post le occurrentia de duo episodios de meningitis acute, con liquido de characteristicas purulente sed sin crescentia in le culturation. Le radiogramma revelava un subjacente defecto cranial. Le sino, su tracto, e un cyste dermoidic intracranial al termino distal esseva excidite chirurgicamente. Le patiente se restabliva completemente.

Depressiones e sinos mesolineal del occipite e in sitos alte supra le axe spinal deberea esser excisionate, particularmente si le radiogramma demonstra un defecto de osso o quando il ha indicios de un augmento del pression intracranial. Le manovra debe includer preparationes pro le entrata in le cavitate cranial, si isto es necessari. Le resultatos ha essite pauco favorabile in patientes con infection, sed le tractamento chirurgic ante le disveloppamento de un infection intracranial es relativemente simple, e on pote expectar que illo va esser coronate de un successo complete.

Basse lesiones in juveniles, specialmente supra le region lumbosacral e le sinos pilonidal, es multo frequente. In le majoritate del casos illos non se extende in ultra del fascia. Lor evalutation debe esser tractate individualmente.

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SALMONELLA TYPHIMURIUM OSTEOMYELITIS WITH SICKLE CELL-HEMOGLOBIN C DISEASE: A REVIEW AND CASE REPORT *

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THE interesting observation has been made [1-10] that salmonella osteomyelitis develops more frequently in patients with sickle-hemoglobinopathies than can be accounted for merely on the basis of chance occurrence.

Osteomyelitis is not a common complication of salmonella infections, since only 0.82% of cases of typhoid fever and 0.2% of paratyphoid infections develop skeletal involvement.[11-15] Of 3,000 cases of salmonella infections (excluding *Salmonella typhosa*) bacteriologically identified by the New York Salmonella Center, only five cultures were obtained from cases of osteomyelitis—three due to *Salmonella typhimurium,* and one each due to *Salmonella enteritidis* and *Salmonella panama.*[16, 17]

In a review of salmonella osteomyelitis published in 1952,[14] only 27 cases of osteomyelitis due to salmonella species other than *Sal. typhosa* or *Salmonella paratyphi B* were collected from the world literature. Seventeen cases were due to *Salmonella suipestifer,* four to *Sal. typhimurium,* four to *Sal. enteritidis,* and one each to *Sal. panama* and *Salmonella oranienburg,* respectively. Other authors [4, 18, 19, 20] have also commented on the rarity of salmonella osteomyelitis.

The true incidence of osteomyelitis in *Sal. suipestifer* infections is somewhat confused by other reports because, in two series of *Sal. suipestifer* infections, a surprisingly high incidence of bone and joint involvement was reported—15%[21] and 50%,[22] respectively—whereas in two other series of *Sal. suipestifer* infections, no cases of bone involvement were noted.[23, 24] In spite of this variation in incidence, there is no doubt that the total of reported cases of *Sal. suipestifer* osteomyelitis is small.

Finally, a study [25] in 1948 demonstrated that salmonella organisms were much less frequently the cause of true hematogenous osteomyelitis than were staphylococci and streptococci.

Bone and joint infections are more common in patients with sickle cell anemia (SS disease) than they are in normal individuals.[26] The bone changes in patients with heterozygous sickle-hemoglobinopathies are similar to, although less extensive and striking than, those in homozygous sickle cell anemia patients.[27] From this, one would also expect a higher incidence of bone infections in cases of heterozygous sickle-hemoglobinopathies than in normal individuals, because the bone changes of marrow hyperplasia, thrombosis, infarction, osteoporosis, and reactive osteosclerosis seen in heterozygous as well as homozygous sickle cell disease [1, 4, 26-30] predispose to the development of superimposed bone infections.[1-4, 10, 28]

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Since the above indicates that salmonella osteomyelitis is relatively rare when compared to common pyogenic osteomyelitis, and that sickle-hemoglobinopathies should predispose to all types of bone infections, it is of great interest that the bone infections which do occur in patients with sickle-hemoglobinopathies are more often caused by organisms of the salmonella group than by the common pyogenic organisms.[1, 5] Hook et al.[3] studied 36 consecutive cases of sickle cell anemia proved by hemoglobin electrophoresis. In their series they found three cases of salmonella osteomyelitis and another case of salmonella bacteremia, yet they reported no cases of osteomyelitis due to staphylococci or streptococci.

Consequently, there seems little doubt of the validity of the clinical impression that sickle cell-hemoglobinopathies predispose to salmonella osteomyelitis. Indeed, it has been suggested[9] that carriers of sickle hemoglobin have a higher incidence of all types of salmonella infections than do people free of sickle hemoglobin. Reports published since the advent of the technic of hemoglobin electrophoresis[1, 2, 4] confirm that cases of heterozygous sickle cell-hemoglobinopathy have a high incidence of salmonella osteomyelitis, as do cases of homozygous sickle cell disease. Finally, as will be pointed out in the discussion, many of the reports in the older literature described cases of salmonella osteomyelitis in patients with "atypical" sickle cell anemia (SS disease) which were, in actuality, probably unrecognized cases of heterozygous sickle hemoglobinopathies.

The following report of a 16-year-old Negro girl who had definite sickle cell-hemoglobin C disease (SC disease) and *Sal. typhimurium* osteomyelitis is the first such case reported in the literature, although a case of sickle cell disease-hemoglobin C disease with *Salmonella infantus* infection has previously been reported.

Case Report

A 16-year-old Negro female was admitted to the Cook County Hospital on March 6, 1959, with the chief complaints of progressively increasing pain, swelling, and tenderness of the right arm and the left thigh, weight loss, and malaise, all of six months' duration.

This patient had lived until the age of 14 on a small farm in Mississippi, and regularly drank unpasteurized milk from cows on that farm. Since infancy she had had intermittent bouts of arthralgia and fever, attributed to "rheumatism." In August, 1958, the patient experienced an episode of acute arthritis and fever which required hospitalization, during which she received three units of whole blood as treatment for her severe anemia. Swelling of the right arm and left thigh developed during the hospitalization, and persisted thereafter.

Approximately two months later the swelling on the medial aspect of the right arm localized and broke down into a purulent, draining sinus. The patient lost 27 pounds (from 106 to 79 pounds). Although she had had menarche at age 15, she developed secondary amenorrhea.

Generalized malaise progressed. The patient sought medical aid, and was treated with one injection of penicillin per week for three weeks, without improvement. She then came to Cook County Hospital and was admitted.

Systemic review failed to reveal any other significant complaints.

The past history was negative except for the above-mentioned anemia, with episodes of arthralgia and fever.

The patient has eight siblings, all of whom are in good health and none of whom has had symptoms suggestive of sickle cell disease. The parents have also been free of such symptoms, although the father has Buerger's disease.

Physical Examination: The patient was a thin young Negro female with a gracile habitus, long extremities, and particularly long, thin phalanges. She was pale and appeared to be chronically ill. There was a low-grade fever (100 to 101° F., orally); pulse, 120/min. and regular; blood pressure, 90/60 mm. Hg.

No abnormalities of the skin were noted. The ears, nose, throat, and eyes presented no abnormalities. Retinal veins were not tortuous. There was generalized, mild, discrete, nontender lymphadenopathy, particularly prominent in the right axilla and right epitrochlear areas. The lung fields were entirely clear, and the examination of the heart was negative.

On examination of the abdomen a firm, nontender spleen was palpated two fingerbreadths below the left costal margin. The liver was not enlarged.

FIG. 1. Osteomyelitis of right humerus.

The right humerus was found to be markedly swollen and tender to palpation. On the medial aspect of the right arm there was a purulent draining sinus surrounded by a localized inflammatory reaction. The left femur was markedly swollen in its transverse diameter, and was tender and irregular on palpation. Although the right femur was tender, it presented no other gross abnormalities on examination.

The rectal and pelvic examinations were negative. Neurologic examination was negative.

Laboratory Findings: Urinalysis was entirely negative, except for a 4-plus Sulkowitch's reaction. The hemoglobin was 8.1 gm. (52%); red blood count, 4,190,000; color index, 0.62. Platelets were adequate. White blood count was 8,200/cu. mm., with 67% polymorphonuclears, 4% bands, 19% lymphocytes, 9% monocytes, and 1% eosinophils. Red cell morphology revealed 2-plus anisocytosis, 1-plus hypochromia, 2-plus targeting, and very slight macrocytosis and polychromatophilia. Two metamyelocytes and one Türk's cell were seen. Frequent subsequent hemograms revealed a gradual increase in the hemoglobin to about 11 gm., with color indices of about 1. Sedimentation rate on admission was 57 mm./hr.

A sickle cell preparation was positive, and hemoglobin electrophoresis revealed a pattern of sickle cell-hemoglobin C disease (SC disease), with 0.6% fetal hemoglobin. Similar studies of the parents and one sister revealed the following:

	Fetal Hemoglobin	Electrophoretic Pattern	Sickle Prep.
Sister	0.8%	AS	?
Mother	0.8%	AS	Positive
Father	0.8%	AC	Negative

Cultures of the purulent material from the sinus of the humerus consistently revealed pure cultures of *Sal. typhimurium*. The organism was sensitive to chloramphenicol, tetracycline, neomycin, and polymyxin B, but was moderately resistant to streptomycin. After prolonged therapy with chloramphenicol, culture of this sinus revealed hemolytic *Staphylococcus aureus*, coagulase-positive. Culture of a sinus on

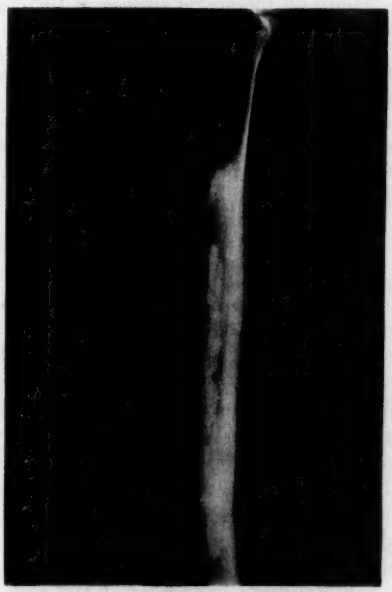

FIG. 2. Osteomyelitis of left femur.

the left thigh, which developed late in the hospital course, also revealed hemolytic *Staph. aureus*, coagulase-positive. Smear and culture of purulent matter failed to reveal acid-fast bacilli or fungi at any time. Cultures of the blood and urine revealed no growth, and no pathogens were isolated on stool culture. Typhoid H agglutination was positive to 1:160, and typhoid O agglutination was positive to 1:80. Paratyphoid A and B and brucella agglutinations were negative. Agglutinations against the organism isolated from the right humeral sinus were positive to 1:320. Serologic test for syphilis was negative. Examination of the stool revealed *Endolimax nana* and *Iodamoeba buetschlii* cysts. Skin tests revealed negative reactions to old tuberculin, 1:10,000, and blastomycin; a histoplasmin skin test was slightly positive.

Fasting blood sugar, blood urea nitrogen, serum calcium, phosphorus, and alkaline phosphatase, cephalin cholesterol flocculation, thymol turbidity, and icterus index were all normal. Serum total protein and albumin were normal, but the

globulin was increased to 4.1 gm.%. Gamma globulin turbidity was also increased. Total cholesterol was slightly low.

The electrocardiogram was normal. X-rays of the right humerus (Figure 1) and the left femur (Figure 2) revealed extensive osteomyelitis. There was moderate cortical thickening of the right femur. X-rays of the chest and abdomen were negative, and a complete bone survey revealed no other lesions.

Management and Course: Following the culture reports indicating *Sal. typhimurium* osteomyelitis the patient was treated with chloramphenicol, 2 gm. per day. Multivitamins, high protein supplemental feedings, and iron were also administered. The patient promptly became afebrile, the toxicity and malaise disappeared, her appetite improved and she gained weight. After one and one-half months the chloramphenicol was discontinued and the patient was transferred to the orthopedic service. In spite of continued clinical improvement, about four months after the patient's admission a new sinus formed on the lateral surface of the distal portion of the left thigh, and hemolytic *Staph. aureus,* coagulase-positive, was cultured from this sinus. Novobiocin, 1 gm. per day, was administered for one and one-half months. Sequestrectomy of the left femur was performed on August 22, 1959, and of the right humerus on September 12, 1959. The patient's postoperative course was uneventful on both occasions. Interestingly, a culture of the right humeral sinus on September 9, 1959, again revealed *Sal. typhimurium* (together with *Pseudomonas aeruginosa*), although this organism had been absent for over four months. Subsequent cultures failed to reveal *Sal. typhimurium.* At the time of discharge the patient was clinically well, but small sinuses persisted on the left thigh and right arm.

Discussion

In addition to cases where the association between salmonella osteomyelitis and sickle cell-hemoglobinopathies has been demonstrated, other cases of salmonella osteomyelitis have been reported where the existence of a hemoglobinopathy was not suspected, but where certain aspects of the clinical picture suggested that a hemoglobin disorder was present. Carrington and Davison [31] reported the first such case in 1925.

Furthermore, many of the cases previously reported as sickle cell anemia were "atypical." Since the advent of chemical and electrophoretic methods for distinguishing the various types of hemoglobins, it has been recognized that many of these cases of "atypical sickle cell anemia" are actually cases that are heterozygous for hemoglobin S and other abnormal hemoglobins. A particularly important type of such heterozygous sickle-hemoglobinopathy is sickle cell-hemoglobin C disease (SC disease).

Myerson et al.[32] demonstrated that the incidence of sickle cell-hemoglobin C disease (SC disease) in Negro patients is 0.1%. In comparison, the incidence in Negro patients of other hemoglobinopathies is as follows: sickle cell anemia (SS disease), 0.4%; sickle cell trait (AS trait), 8.5%; hemoglobin C trait (AC trait), 2.2%; homozygous hemoglobin C disease (CC disease), less than 0.1%.[32] Although other heterozygous sickle hemoglobinopathies do occur (sickle cell-hemoglobin D disease [SD disease], sickle cell-hemoglobin G disease [SG disease], etc.), they are of such rarity as to be of lesser importance. Smith and Conley [27] thoroughly studied the differences in the clinical pictures produced by the genetic variants of sickle cell disease. They demonstrated that cases of sickle cell-hemoglobin C disease (SC disease) may have almost all of the manifestations of sickle cell anemia (SS disease), but that, in general, these manifestations are less frequent and less severe than in sickle cell anemia (SS disease).

TABLE 1

Authors & Reference Numbers	Year	Case No.	Organism Isolated (all cases of osteomyelitis unless otherwise indicated)	Homozygous Sickle-Cell Anemia	Heterozygous Sickle-Cell Hemoglobinopathy
Carrington and Davison[31]	1925	1	*B. paratyphosus B*		8-yr.-old Negro male with splenomegaly, marked anemia. Possible crises in preceding 8 months. No mention of sickling on routine smears.
Veal and McFetridge[15]	1934	2	*B. paratyphosus B*		Possible case, 3-yr.-old Negro male. Markedly anemic. No mention of sickling on routine blood smear.
		3	*B. paratyphosus B*		Possible case, 8-yr.-old Negro male. Possible crises for 3 years. No mention of anemia.
Diggs, Pulliam, and King[26]	1937	4	Paratyphoid B arthritis	"Definite sickle cell anemia." No details given.	
Seidenstein[32]	1945	5	"Salmonella group"	13-yr.-old Negro female. Marked anemia. "Sickling of red cells seen in blood smear."	
Burch[34]	1949	6	Paratyphoid B		15-yr.-old Negro male. Anemic. Splenomegaly. Sickle cell prep. "positive." No mention of sickling on direct smear.
Wigh and Thompson[35]	1950	7	*B. paratyphosus B*	14-yr.-old Negro male. Three previous admissions for definite sickle cell anemia. Multiple transfusions.	
Mayer and Pohlidal[36]	1951	8	*Sal. montevideo* septicemia. and later osteomyelitis		27-yr.-old Negro male with splenomegaly and hepatomegaly. No sickling noted at age 24, but 100% sickling noted at age 25 (on prep.?). No details about blood counts given.
Holt and Hodges[10]	1951	9 10 11 12 13	Paratyphoid B, all cases	All cases stated to be sickle-cell anemias. No details given.	
Traisman and Champlin[18]	1951	14	*Sal. typhimurium*	14-month-old Negro female. Marked anemia with 100% sickling on prep. in 4 hours.	
Ehrenpreis and Schwinger[29]	1952	15 16	"Salmonella group"	Stated to be classic cases with active sickling within 1 hour on prep. Cases of trait eliminated.	
Smith[28]	1953	17	"Salmonella organism"	9-yr.old Negro female. 5 yr. history of crises. Pronounced sickling in 15 minutes on sealed wet prep., but spleen mildly enlarged.	
		18	*Sal. suipestifer*	6-yr.-old Negro female. Sickling in 15 minutes on wet sealed prep. Spleen enlarged.	
		19	"Gram-neg. rod of paracolon group"	20-yr.-old Negro female. Almost 100% sickling on wet sealed prep. Only two previous crises.	

TABLE 1—*Continued*

Authors & Reference Numbers	Year	Case No.	Organism Isolated (all cases of osteomyelitis unless otherwise indicated)	Homozygous Sickle-Cell Aneima	Heterozygous Sickle-Cell Hemoglobinopathy
Zuelzer[37]	1953	20 21	"Salmonella organisms"	Both said to be cases of "sickle-cell anemia." No details given.	
Vandepitte, Colaert, Lambotte-Legrand, and Perin[7]	1953	22	*Sal. typhimurium*	11-yr.-old Negro male. "Sickle-cell anemia."	
		23	*Sal. typhimurium*	15-month-old Negro female. "Sickle-cell anemia."	
		24	*Sal. kisangani*	9-month-old Negro male. "Sickle cell anemia."	
		25	*Sal. typhimurium*	2½-yr.-old Negro female. "Sickle-cell anemia."	
		26	*Sal. leopoldville*	6-yr.-old Negro male. "Sickle-cell anemia."	
Ellenbogen, Raim, and Grossman[38]	1955	27	*Sal. montevideo*	27-month-old Negro male. Marked anemia. 25% to 85% sickling on preps. Previous blood transfusions.	
Choremis, Yannakos, and Bonta[39]	1955	28	"Typhoid paratyphoid group"		7-yr.-old child. Case from University Children's Clinic of Athens, but race not stated. Anemic. "Sickle-cell test positive." Target cells seen on smear.
		29	"Probably typhoid group"		6-yr.-old child. Case from University Children's Clinic of Athens, but race not stated. Marked anemia. "Sickle-cell test positive." "Alkaline resistant, hemoglobin, 20.8%." Father, "heterozygous sickle disease with positive sickle cell test." Mother, "Cooley-trait."
Goldenberg[19]	1955	30	*Sal. enteritidis* (osteomyelitis and remote postop. wound infection)		11-yr.-old male of Sicilian parents. "Thalassemia Major with sickling demonstrated at age 7." Only moderate anemia on admission. Splenomegaly. 75% sickling after 22 hours on prep.
Giaccai and Idriss[14]	1952	31	*Sal. enteritidis*		6-yr.-old Arabian female. Marked anemia, "probably hemolytic crises" with joint pains. No sickle cell preps. No mention of sickling on direct smears.
White and Meynell[20]	1956	32	*Sal. paratyphi C*		Possible case. 40-yr.-old Jamaican male. Not anemic. Nothing to suggest hemoglobinopathy other than salmonella osteomyelitis.
Vandepitte and Van Oye[8] (quoting previous work by Vandepitte and Colaert)	1956	—	Organism not cultured, but pt. had osteomyelitis		"Sickle cell-C disease" (SC).

TABLE 1—*Continued*

Authors & Reference Numbers	Year	Case No.	Organism Isolated (all cases of osteomyelitis unless otherwise indicated)	Homozygous Sickle-Cell Anemia	Heterozygous Sickle-Cell Hemoglobinopathy
Hughes and Carroll[5]	1957	33	*Sal. typhimurium*	Infant Negro male. Marked anemia. Sickling on direct smear. Sickle cell crises.	
		34	*Sal. schottmülleri*	4-yr.-old Negro male. "Immediate sickling of erythrocytes . . . Known sickle cell disease."	
		35	*Sal. schottmülleri*	3-yr.-old Negro male. Sickling on direct blood smear. "Sickle cell disease."	
		36	"Salmonella organism"	3-yr.-old Negro male. Marked anemia. "Sickle cell disease."	
Silver, Simon, and Clement[4]	1957	37	*Sal. enteritidis* (osteomyelitis and remote postop. wound infection)		11-yr.-old white male. Sickle cell-thalassemia. Anemia, splenomegaly, anisocytosis, poikilocytosis, polychromatophilia, target cells, "50% sickling."
		38	*Sal. typhimurium*		3-yr.-old Negro female. Hemoglobin CD disease proved by hemoglobin electrophoresis. 10% target cells. Moderate anisocytosis and poikilocytosis. No sickling.
Hook, Campbell, Weens, and Cooper[4]	1957	39	*Sal. paratyphi B*	15-month-old Negro male. SS disease proved by hemoglobin electrophoresis.	
		40	*Sal. typhimurium*	3-yr.-old Negro male. SS disease proved by hemoglobin electrophoresis.	
		41	*Sal. typhimurium*	22-yr.-old Negro male. SS disease proved by hemoglobin electrophoresis.	
		—	*Sal. choleraesuis* (septicemia, no osteomyelitis)	23-yr.-old Negro male. SS disease proved by hemoglobin electrophoresis.	
Roberts and Hilburg[1]	1958	42	Salmonella sp. (type bredeney)	7-month-old Negro female. SS disease. "Known to be homozygous for sickle cell disease."	
		43	*Sal. typhimurium*	15-month-old Negro female. SS disease. "Known to be homozygous for sickle cell disease."	
		44	Salmonella sp. (type oranienburg)	4-yr.-old Negro male. "Sickle cell disease."	
		45	Salmonella sp. (type infantus)		11-yr.-old Negro male. SC disease, proved by hemoglobin electrophoresis.
Widen and Cardon	1959	46	*Sal. typhimurium*		16-yr.-old Negro female. SC disease, proved by hemoglobin electrophoresis.

Table 1 is a summary of a review of the literature of cases of salmonella osteomyelitis occurring in association with hemoglobin disorders. Included are not only cases of homozygous sickle cell disease, but also definite and possible cases of heterozygous sickle cell hemoglobinopathies, and one definite case of a nonsickle hemoglobin disorder (case 38—hemoglobin C-hemoglobin D disease [CD disease]). This series of 46 cases is larger than others recently reported,[1, 3, 4] in part because of the inclusion of these various types of cases. We have omitted the bony sites of the osteomyelitis and certain details of the blood picture in the interest of brevity. Suffice it to say that, in the great majority of these cases, there were multiple sites of osteomyelitis, with particular predisposition to the long bones of the extremities, especially the humeri and femora.

Perusal of the table reveals several interesting facts. First, of the 46 cases presented, 32 are classified as being cases of homozygous sickle cell anemia. However, in eight cases (cases 4, 9–13, 20, and 21), no details other than the statement "sickle cell anemia" are available. In addition, in cases 17 and 18 the diagnosis was based on sickling present in a sealed wet preparation. These two cases were children, aged nine and six years, respectively, and both had splenomegaly. Therefore, the *possibility* exists that these are really cases of sickle cell-hemoglobin C disease (SC disease).

Second, 14 of the cases are classified as heterozygous sickle cell-hemoglobin disorders (or other hemoglobinopathies). However, only three of these have been proved by hemoglobin electrophoresis. Two (cases 45 and 46) had sickle cell-hemoglobin C disease (SC disease), and one (case 38) had hemoglobin C-hemoglobin D disease (CD disease). Cases 30 and 37 undoubtedly had sickle cell-thalassemia. Three other cases were included as possible hemoglobin disorders (cases 2, 3, and 32), although admittedly the inclusion of cases 3 and 32 is highly questionable, being based only on the race of the patient and the presence of known salmonella osteomyelitis. The other six (cases 1, 6, 8, 28, 29, and 31) were listed as probable heterozygous sickle cell-hemoglobin disorders for the reasons listed in the table. In view of the atypical features of each of these cases, such classification seems warranted.

Finally, the majority of the cases with true sickle cell anemia were infants and children, whereas the heterozygous sickle cell-hemoglobin disorders generally occurred in older children.

From the above it seems justified to state that salmonella osteomyelitis probably occurs in association with various hemoglobin disorders in which sickle-hemoglobin is present. Although most cases occur in sickle cell anemia, and in the past were reported predominantly in the pediatric literature, older patients with heterozygous sickle-hemoglobinopathies and salmonella osteomyelitis should in the future come to the attention of internists, since such heterozygous hemoglobin disorders may be attended by little or no disability, and the life span may not be shortened. With the technic of hemoglobin electrophoresis, the exact hemoglobin pattern in such cases should be elucidated. As a corollary, it would seem that any patient presenting with salmonella osteomyelitis deserves hemoglobin electrophoretic studies, whether anemia is present or not.

Several authors[1–4, 7, 28] have presented possible explanations for the pathogenesis of the association between salmonella osteomyelitis and sickle cell-hemoglobin diseases. It has been pointed out that small injuries to the intestinal wall

resulting from localized thromboses in cases of sickle-hemoglobinopathies may allow for easier passage of intestinal organisms, including salmonellae, into the bloodstream. Salmonellae tend to persist in the bone marrow even after other sites become sterile. Because the bone changes seen in both homozygous and heterozygous sickle cell disease predispose to the establishment of infection, the salmonellae in the bloodstream and bone marrow are more likely to produce true osteomyelitis.

As early as 1937, Diggs et al.[26] pointed out the difficulties in the diagnostic differentiation between sickle cell anemia (SS disease) in crisis with bone and joint pain, and sickle cell enemia (SS disease) with superimposed true osteomyelitis. Other authors have commented on this.[1-4, 28, 38] The radiologic picture of the bones in sickle cell anemia (SS disease) may mimic closely the radiologic picture of osteomyelitis. Since in sickle cell crisis as well as in osteomyelitis there may be fever, bony pain, leukocytosis, and swelling of the extremities, the diagnosis of osteomyelitis might be overlooked, and the entire clinical picture be attributed to sickle cell crisis. In view of the association between sickle cell disease and salmonella osteomyelitis, the latter should always be considered.

Summary and Conclusions

A case is reported of *Sal. typhimurium* osteomyelitis in a 16-year-old Negro girl with sickle cell-hemoglobin C disease (SC disease). This is the first such case in the literature, and the second case of any salmonella osteomyelitis occurring in a patient with sickle cell-hemoglobin C disease (SC disease).

Review of the literature confirms the clinical impression that there is a definite association between salmonella osteomyelitis and homozygous and heterozygous sickle cell hemoglobinopathies. Pathogenetic explanations for this association have been presented.

Since heterozygous sickle cell-hemoglobinopathies and other hemoglobin disorders may be entirely silent clinically, patients presenting with salmonella osteomyelitis deserve hemoglobin electrophoretic studies. The difficulty in distinguishing sickle cell crisis with bony pain from superimposed osteomyelitis should be borne in mind.

Summario in Interlingua

In patientes con falci-hemoglobinopathias, il existe un interessante predisposition pro le contraction de osteomyelitis a salmonella. Osteomyelitis per salmonella es pauco commun, e mesmo in osteomyelitis hematogene, organismos de salmonella es minus frequentemente le agentes etiologic que staphylococcos e streptococcos. Ben que omne typos de infection ossee e articular es plus commun in patientes con falci-hemoglobinopathias que in subjectos normal, infectiones ossee in patientes con falci-hemoglobinopathias es plus frequentemente causate per organismos del gruppo de salmonella que per le commun organismos pyogene. Le pathogenese de iste predisposition es explicate.

Le autores reporta un caso de osteomyelitis a *Salmonella typhimurium* in un puera negre de 16 annos de etate qui definitemente habeva morbo falciforme a hemoglobina C. Isto es le prime tal caso reportate in le litteratura. Un revista del litteratura ha monstrate que osteomyelitis a salmonella occurre in association con falci-hemoglobinopathias heterozygotic si ben como in association con anemia a cellulas falciforme homozygotic, ben que le majoritate de tal casos es incontrate in patientes con anemia a cellulas falciforme. Per consequente, in le passato tal casos

esseva reportate predominantemente in le litteratura pediatric. Viste que disordines heterozygotic de hemoglobina pote occurrer con pauc o nulle invaliditate e que in lor presentia le longevitate del patiente non es necessarimente reducite, patientes de etates plus matur con falci-hemoglobinopathias heterozygotic e osteomyelitis a salmonella va sin dubita esser notate in le futuro per le internistas. Pro iste ration, omne patiente qui se presenta con osteomyelitis per salmonella merita studios electrophoretic de hemoglobina, sin reguardo a si anemia es presente o non.

Finalmente, le difficultate de distinguer inter crises de morbo a cellulas falciforme con dolores ossee e un superimponite osteomyelitis non debe esser negligite.

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MULTIPLE HEMATOLOGIC ABNORMALITIES IN A CASE OF POSTNECROTIC CIRRHOSIS *

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A GREAT variety of hematologic disturbances may be associated with hepatocellular disease. There is no close correlation between the histopathology of

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the liver disease and the variety or degree of hematologic disorder. Several clinicopathologic reviews of postnecrotic cirrhosis of the liver have appeared,[1-4] but generally few details regarding the hematologic picture in this disorder are given. It is the purpose of this paper to report a case of postnecrotic cirrhosis which manifested hemolytic anemia, fibrinolysis, lymphocytosis, and abnormalities in hemoglobin synthesis.

TABLE 1
Liver Function Tests

Date	Urine		Serum					BSP Retention
	Urobilinogen (Ehrlich Units)	Porphobilinogen	Bilirubin (Direct/Total)	Alk. Phos.	Ceph. Floc.	Thym. Turb.	A/G	
3-21-57	0.233	—	1.5 total	—	4+	11.9	5.7/2.8	—
3-28-57	1.5	—	0.0/0.3	7.05	4+	—	—	—
4- 1-57	—	—	0.65/1.71(17.2)*	—	—	—	—	—
4- 4-57	—	—	(75)*	—	—	—	—	—
4- 8-57	—	—	—	—	—	—	3.4/5.0	53%
5- 7-57	0.34	—	0.86/1.5 (14.5)*	9.3	—	—	3.7/4.0	—
5-28-57	—	—	—	—	—	—	—	27.5%
8- 6-57	—	—	2.4/3.6	14.1	1+	—	4.1/4.3	—
11- 4-57	1.0	—	1.9/3.9	10.8	4+	—	4.6/3.4	—
11- 8-57	—	—	—	—	—	—	—	9.9%
1- 6-58	—	—	2.5/3.7	—	—	—	—	—
1-16-58	—	—	4.5/6.4	8.7	3+	—	4.4/2.0	—
1-27-58	—	—	1.6/5.2	—	—	—	—	51%
1-28-58	0.5	—	6.0/13.8	—	—	—	—	—
2- 5-58	—	—	11.3 total	—	—	—	—	—
2-19-58	—	Pos.	—	—	—	—	—	—
2-20-58	0.40	Neg.	3.9 total	—	—	—	—	46.9%
2-21-58	—	Neg.	1.9/3.0	—	—	—	—	—
3-13-58	0.05	Neg.	5.8 total	—	4+	—	—	59.4%
5-12-58	—	—	2.0/3.6	—	4+	—	—	—
5-19-58	0.40	—	1.3/4.0	—	—	8.8	—	—
6-19-58	0.25	Neg.	2.3/6.0	—	4+	16	3.1/4.2	—
6-20-58	0.20	Strongly pos.	—	—	—	—	—	—
6-24-58	0.60	Pos.	—	—	—	—	—	—
7- 9-58	—	—	5.1/9.5	—	—	—	—	—

* Icteric index.

CASE REPORT

A 45-year-old white male was admitted to the City of Hope Medical Center in March, 1957, complaining of episodic hemoptysis of 14 years' duration. This had become increasingly frequent just prior to admission. The episodes usually lasted several days, producing a half cupful of bright red blood with dark clots daily. There were no other pulmonary symptoms. Prior to admission, bronchoscopy had revealed a distinct bleeding point in the medial basal segment of the left lower lobe bronchus. Family and past history was noncontributory. The patient was a light smoker and drank alcoholic beverages sparingly. He had suffered from intermittent nose and gum bleeding, as well as intermittent leg pains and paresthesias of the fingertips.

First Admission: On physical examination the patient was not in distress. Blood pressure, 150/80 mm. Hg. The only abnormal findings were a soft precordial systolic murmur and slight clubbing of the fingers and toes. Chest x-ray showed increased bronchovascular markings in both bases, but bronchograms and planigrams were

TABLE 2

Hematologic Studies

Date	WBC	Hct.	Retic.	Platelets	% Lymphs	ESR
3-20-57	6,900	31	—	—	62	—
4- 1-57	9,350	26	—	—	—	—
4- 4-57	—	34	0.8%	—	—	—
5- 7-57	6,600	37	—	—	71	—
6- 5-57	4,500	37	—	—	60	—
7-17-57	6,900	36	—	—	54	—
8-28-57	6,750	35	—	40,000	57	—
11- 4-57	5,300	36	1.4%	87,500	57	—
11-14-57	6,250	33	—	122,500	59	—
1-14-58	7,050	29	—	80,000	41	—
1-20-58	11,050	25	—	116,000	34	—
1-22-58	8,100	27	—	Mkd. red.	30	—
2- 4-58	—	32	0.5%	—	—	—
2-21-58	7,450	30	—	—	64	9
3-24-58	7,700	33	—	Adequate	45	—
4-14-58	7,950	31	1.8%	Adequate	56	—
5-12-58	10,900	32	2.3%	Mod. red.	11	30
6- 6-58	7,500	27	—	Decreased	52	—
6-16-58	—	41	6.3%	—	—	—
6-19-58	14,050	37	7.0%	Adequate	32	28
6-23-58	—	34	2.6%	71,250	—	—
7- 7-58	—	38	3.7%	26,250	—	—

negative. The electrocardiogram showed myocardial ischemia. Hematocrit, 31; white blood cell count, 6,900/cu. mm., with 62% lymphocytes. Blood type was O, Rh positive. Fibrinogen, 200 mg.%; prothrombin time, 15 seconds. The liver function tests on this and subsequent admissions are shown in Table 1. Evidence of disturbed function was already present. Bronchoscopy and esophagoscopy were normal. Bone marrow study showed a hypocellular marrow with occasional erythrophagocytosis.

The patient was given a blood transfusion (type O, Rh positive) and developed a shaking chill after receiving 200 ml. Another transfusion of O-positive blood was followed by a temperature spike of 39.2° C. The liver edge was felt three finger-breadths below the costal margin at this time. There were a transient albuminuria and a urobilinogenuria of 1.5 Ehrlich units, and the bilirubin rose to 1.7 mg.%. There was no rise in hematocrit. Four days later, 500 ml. of O-negative blood were given, without serious sequelae. Subsequent study revealed that the patient's blood type was CdE, and that he had been typed "Rh positive" erroneously.

TABLE 3

Coagulation Studies

Date	Bleed. Time	Coag. Time	Clot Retract. (1 hr.)	Clot Lysis Complete by	Platelets	Quick Time	Proaccelerin	Proconvertin	Prothrombin	Prothr. Cons. (1 hr.)
10-30-57	4′	9′	Good	6 hrs.	98,750	16.3″(35%)	38%	61%	51%	88%
11- 4-57	—	6′	Good	<24 hrs.	87,500	—	—	—	—	—
11-11-57	—	8′	Good	3 hrs.	83,750	15.2″(44%)	54%	60%	70%	82%
11-13-57	—	9′	Good	3 hrs.	140,000	16.5″(34%)	36%	55%	50%	90%
12- 9-57	—	10½′	Good	18 hrs.	68,750	15.6″(40%)	38%	55%	48%	90%
1-14-58	5′	8′	Good	<24 hrs.	80,000	20.0″(20%)	10½%	26½%	33%	91%
1-17-58	—	—	—	—	77,500	17.1″(30%)	24%	45%	40%	—
1-20-58	—	—	—	—	116,000	17.5″(25%)	30%	41%	50%	—
2-19-58	—	6′	—	24 hrs.	—	—	—	—	—	—
6-23-58	—	6′	Poor	6 hrs.	71,250	16.4″(35%)	35%	34%	44%	70%

Following discharge, the patient remained clinically well until November, 1957. Hematologic values were normal except for a persistent lymphocytosis (Table 2). Red cell fragility was normal, and two L.E. preparations were negative. In October he bled profusely for five days from a trivial cut of the finger. A painful ecchymotic area developed over one calf and became fluctuant. When lanced by the family physician, this also bled for five days. A platelet count of 40,000 was found. Bleeding time was 6½ minutes. Bone marrow aspiration, performed on October 30, 1957, was moderately hypercellular, with increased erythropoiesis. Granulopoiesis was active. Many myelocytes showed heavy basophilic granules. Megakaryocytes were adequate in number and normal in appearance. There was a slight plasmacytosis. A battery of coagulation tests was performed (Table 3). The patient was started on prednisolone, 15 mg. daily.

Second Admission: Six days later the patient began to bleed profusely from the site of the marrow puncture and was readmitted to the hospital. Physical examination revealed scattered telangiectasia over the face and neck. The liver edge was palpable two fingerbreadths below the costal margin, but the spleen could not be felt. There was bleeding from the bone marrow aspiration site. Blood counts were unchanged (Table 2). Reticulocytes were 1.4%. The Coombs' test (direct and indirect) was negative, but cold agglutinins were present in a dilution of 1:16.

The bleeding marrow puncture site was treated with topical thrombin and Gelfoam, and was eventually controlled. The patient was discharged after 10 days on prednisolone, 15 mg. daily. For about two days in December, 1957, he had a period of mental confusion associated with an upper respiratory infection. Neurologic examination revealed slow nystagmus on left lateral gaze, and hyperactive reflexes with positive Hoffmann's and Babinski's signs bilaterally. Ankle clonus was present bilaterally. He complained of paresthesia of both hands, but no sensory changes were found.

Third Admission: On January 13, 1958, severe hemoptysis recurred and the patient was readmitted. Bright red blood was noted in the mouth and oropharynx, but no bleeding site could be determined. Aside from slurred speech and inappropriate affect, physical findings were unchanged. The spinal fluid culture was negative. The cold agglutination test was negative on this occasion, as was Ham's acid hemolysis test. Electroencephalogram showed a diffuse abnormality without evidence of focal neurologic disease. Skull films were negative, and a skin and muscle biopsy was not diagnostic.

Despite treatment with intravenous vitamin K_1 oxide, bleeding persisted intermittently during the next few days. The patient received two units of blood, but the hematocrit fell progressively to 24. The prednisolone, which had been discontinued, was resumed in a dosage of 45 mg. daily. The bleeding ceased, and there was a gradual rise of the hematocrit back to normal levels. On February 4, 1958, rather marked icterus developed, with a maximal bilirubin concentration of 14.9 mg.%.

Special laboratory studies: Urinary amino acid and copper excretion was normal. Blood ammonia was 2.2 mg.%. X-ray studies of the gastrointestinal and urinary tracts were negative. The patient was discharged on February 8, 1958, on prednisolone, 45 mg. daily, which was discontinued after one month.

Fourth Admission: A brief hospitalization was required in February, 1958, because of drowsiness and somnolence. Porphobilinogen was first noted in the urine during this admission. The prednisolone was started again, in a dosage of 15 mg. daily.

Fifth Admission: On May 10 the patient was readmitted because of fever, semicoma, and bleeding from the urethra and gums. The temperature was 39.5° C.; pulse, 128. The patient was comatose and appeared to be acutely ill. Hemolytic *Staphylococcus aureus,* coagulase-positive, was cultured from the blood, urine, and

nasopharynx. After the second day of treatment with large doses of antibiotics and steroids, there was gradual improvement, and the patient was discharged after 16 days. During this hospitalization, serum electrophoresis revealed albumin, 28%; $alpha_1$ globulin, 4.5%; $alpha_2$ globulin, 7%; beta globulin, 7.7%; gamma globulin, 52.8%.

During the ensuing month the patient was continued on methylprednisolone, 30 mg. daily, and followed on an anti-ulcer regimen. The hematocrit rose to 41, and a reticulocytosis of 6.3% was noted. Serum bilirubin remained elevated.

Sixth Admission: On June 18, 1958, the patient was readmitted because of another episode of increasing confusion, nausea, vomiting, fever, and semicoma. Crackling râles were heard over both bases. Throat culture showed beta hemolytic

FIG. 1. Liver. The coarse nodular lobulation is particularly noticeable in the left lobe.

streptococcus. Urine culture showed *Aerobacter aerogenes.* Cultures of the spinal fluid and blood were negative. There was a leukocytosis with essentially normal differential, and a reticulocytosis of 7%. The patient was treated with intravenous penicillin and Chloromycetin in large doses, and with intramuscular prednisolone. There was a gradual improvement, with defervescence and mental clearing. The patient was discharged after one week, much improved.

Special laboratory studies revealed a low serum copper (0.02 mg.%), slightly elevated ceruloplasmin (12 units; normal, 5 to 10.8 units), and normal serum iron (153 μg.%), and iron-binding capacity (290 μg.%). The urine porphobilinogen test was positive on two occasions and negative on another. Urine copper was 0.08 mg./L.; coproporphyrin, 176 mg./24 hrs., delta-aminolevulinic, 4.1 mg./24 hrs.; uroporphyrin, negative. Coagulation studies were essentially unchanged from those previously reported.

Seventh Admission: The patient was readmitted on July 5, 1958, because of fever and hemoptysis during the previous three days. He appeared to be acutely ill,

although well oriented and responsive. The sclerae were icteric, and a pleural friction rub and râles were heard over the right posterior base. There was no cyanosis or edema. Clubbing of the fingers and toes was marked. Temperature was 38.4° C. Chest x-ray showed consolidation of the right lower lobe. Sputum and blood cultures again revealed *Staph. aureus,* coagulase-positive. Therapy with Chloromycetin and penicillin was begun, but the patient failed to respond. He became lethargic, confused, and incoherent, lapsed into a coma, and died on July 10, 1958.

Post-mortem Examination *

Gross Description: The interventricular septum showed an area of flame-shaped subendocardial hemorrhages, measuring 3 by 2 cm. The right lower lobe showed pneumonic consolidation, with a poorly defined abscess cavity measuring 6 cm. in diameter.

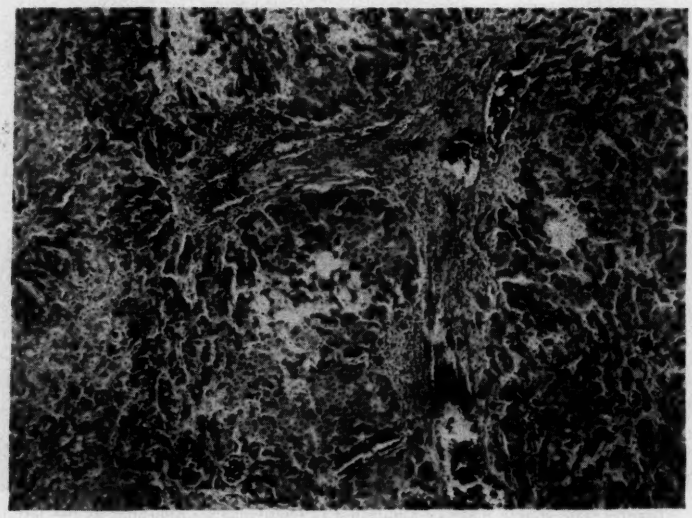

FIG. 2. Liver. Hematoxylin and eosin, × 25. Marked disruption of architecture, with dense fibrous septa forming an irregular pattern.

The liver weighed 980 gm. Its capsule was irregular. It was coarsely lobulated, particularly the left lobe (Figure 1.) The liver was firmer than normal, and discolored a green-gray. On section, broad, irregular gray scars, up to 10 cm. in length, replaced much of the liver parenchyma. The remainder of the liver consisted of yellow-green nodules of varying size, separated by fibrous-like tissue. The gallbladder and extrahepatic ducts were free of change.

A large mass of varicosities, approximately 15 cm. in diameter, was present at the splenic hilum, extending into the splenic ligament and down along the descending mesocolon. Petechial hemorrhages were present in the left renal pelvis.

The esophagus was free of abnormalities, and there were no visible varicosities. Except for dark red-purple subserosal ecchymoses of the jejunum, the gastrointestinal tract was free of abnormalities.

* The post-mortem was performed by Dr. George Amromin, Director, Department of Pathology.

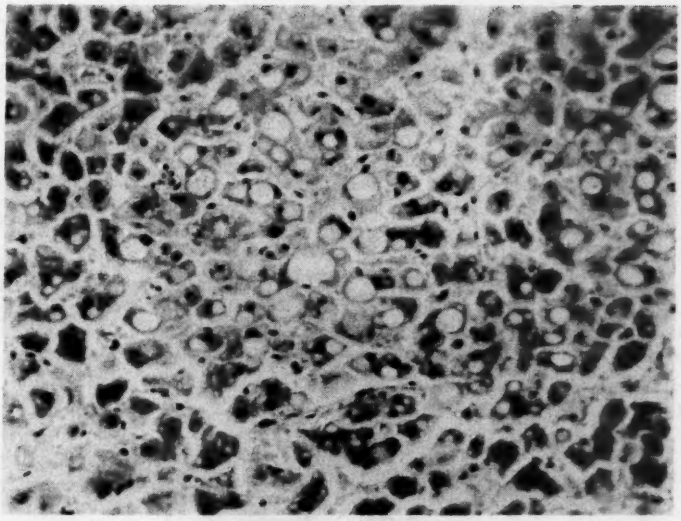

FIG. 3. Liver. Hematoxylin and eosin, × 120. Area of active necrosis, with fatty degeneration of parenchymal cells.

There were hemorrhagic areas in the right internal capsule of the brain, in the left occipital lobe and in the right cerebellar hemisphere, and scattered beneath the pia.

Microscopic Description: The myocardial fibers were separated by clear spaces,

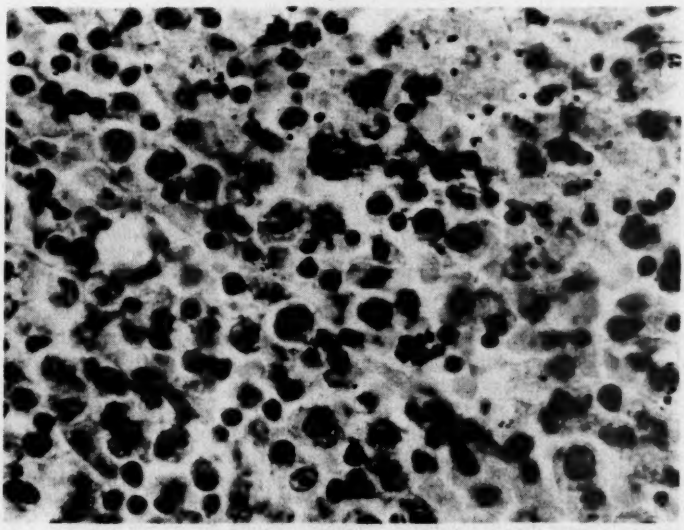

FIG. 4. Bone Marrow. Hematoxylin and eosin, × 400. The marrow is hypercellular, with increased erythroid precursors.

and there were areas of interstitial hemorrhage. In the lungs, many of the alveolar spaces were filled with granular-appearing eosinophilic material and collections of nuclear debris. Numerous aggregates of branching, thick-walled mycelia resembling Aspergillus were seen.

The liver architecture was distorted and irregular. In most areas, normal lobules were absent, and instead there were groups of liver cells surrounded by thin fibrous tissue septa (Figure 2.) Occasional aggregates of monocytic cells were present. The sinusoids, where they could be identified, were hyperemic. Many liver cells, particularly in the centrilobular portions, showed clear vacuoles of variable size in their cytoplasm (Figure 3.) Small groups were completely destroyed. A silver

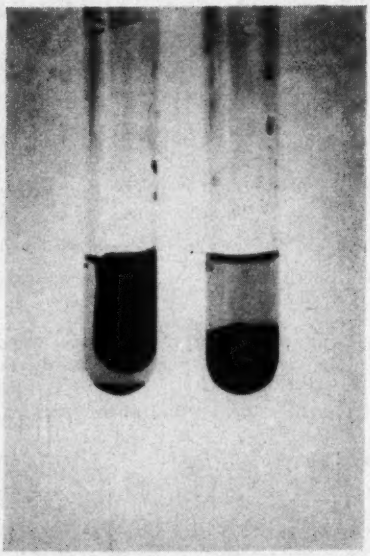

FIG. 5. Left: normal control; right: patient. The patient's clot has completely dissolved. The red cells have fallen to the bottom of the tube.

stain demonstrated irregular condensations of argentophilic fibers, particularly in the peripheral portions of the lobular remnants. The splenic pulp was markedly congested, and there were scattered groups of plasma cells.

Bone marrow was very cellular (Figure 4). Megakaryocytes were present and appeared to be normal.

Investigative Methods: The coagulation tests used in this investigation have been described previously.[5] Special tests of fibrinolysis were done according to several different methods. In addition to simple observation of clotted whole blood, the indirect clot lysis method of Stefanini and Dameshek [6] and the method of Biggs and Macfarlane [7] were used.

Plasma was fractionated with the Spinco continuous curtain electrophoresis apparatus.* The resultant dilute plasma fractions were tested for fibrinolytic activity by the indirect method, and then concentrated by dialysis overnight against 30% PVP, and retested for activity.

Many tests were done repeatedly. Typical results are given.

* Kindly performed by Dr. Burroughs Hill, of the Department of Biochemistry.

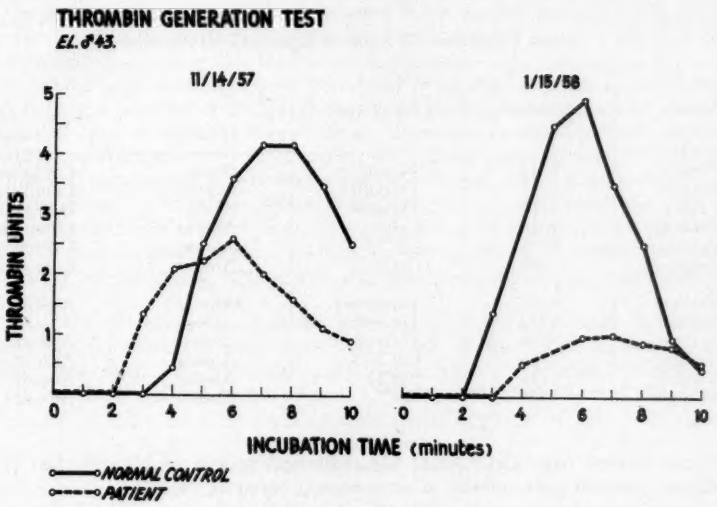

FIG. 6.

Results: Lysis of the clotted whole blood was found on repeated occasions. The time at which the clot lysed varied between three and 24 hours. This phenomenon was found on every occasion that it was sought. Lysis of the clot was always complete (Table 3 and Figure 5).

As shown in Table 3, a multiplicity of disturbances of the coagulation mechanism was repeatedly noted. A moderate to severe thrombopenia was always present. The prolonged Quick time was found to be due primarily to a marked reduction of proaccelerin. Prothrombin and proconvertin levels were moderately depressed. Despite the thrombopenia, the consumption of prothrombin was frequently normal (90% or higher). Fibrinogen was 200 and 190 mg.% on two different occasions. The low levels of the coagulation factors were not due simply to the action of the fibrinolysin, because when a sample of the patient's serum was incubated for 48 hours with normal plasma, no significant change in the levels of any of the coagulation factors was noted.

Thrombin generation was tested on two occasions and was markedly depressed when compared to that of a normal control (Figure 6). This is most readily explained on the basis of the coexistent thrombopenia.

The thromboplastin generation test gave abnormal results when all reagents

TABLE 4

Thromboplastin Generation Test

Source of:			Incubation Time						
$Al(OH)_3$ Plasma	Serum	Platelets	1′	2′	3′	4′	5′	6′	8′
Normal	Normal	Normal	50″	47″	25″	12″	10″	—	11″
Patient	Patient	Patient	50″	46½″	26″	17½″	16″	14″	14″
Patient	Normal	Normal	50″	34½″	14″	11″	11″	10″	—
Normal	Patient	Normal	50″	50″	38″	23½″	14″	9″	11″
Normal	Normal	Patient	50″	50″	43″	24½″	17½″	12½″	14″

TABLE 5

Plasma Clot Lysis (Method of Biggs and Macfarlane)

Plasma	Dilution	Clotting Agent	Lysis	
			1½ Hours	5 Hours
Patient	1/16	Thrombin	Slight	Complete
Patient	1/32	Thrombin	Slight	Complete
Patient	1/64	Thrombin	Slight	Complete
Patient	1/16	$CaCl_2$	Absent	Complete
Patient	1/32	$CaCl_2$	Absent	Complete
Patient	1/64	$CaCl_2$	Absent	Complete
Normal	1/16	Thrombin	Absent	Absent
Normal	1/32	Thrombin	Absent	Absent
Normal	1/64	Thrombin	Absent	Absent
Normal	1/16	$CaCl_2$	Absent	Absent
Normal	1/32	$CaCl_2$	Absent	Absent
Normal	1/64	$CaCl_2$	Absent	Absent

used were derived from the patient, but individual testing of his adsorbed plasma, serum, and platelets gave normal or near-normal results (Table 4).

The patient's plasma and serum both lysed a dog fibrin clot within 24 hours when tested undiluted. When the patient's own dilute plasma was clotted, by the addition of either thrombin or M/20 $CaCl_2$, clot lysis occurred within from five to 24 hours (Table 5).

TABLE 6

Attempts to Characterize the Fibrinolysin

Material Tested	Lysis			
	4 hours	8 hours	24 hours	48 hours
Plasma (fresh)	0	0	0	0(++, 72 hrs.)
Plasma (stored 24 hrs. at 4°)	0	0	+	+++
Plasma (stored 24 hrs. at RT)	0	0	+	+++
Plasma (stored 48 hrs. −10°)	0	0	+++	
Serum (fresh)	0	0	0	+(+++, 72 hrs.)
Serum (stored 24 hrs. at 4°)	0	0	0	+++
Serum (stored 24 hrs. at 37°)	0	0	§	
Serum (stored 48 hrs. at −10°)	0	0	0	
Plasma adsorbed with $BaSO_4$	0	+++		
Plasma adsorbed with $Al(OH)_3$	0	+++		
$(NH_4)_2SO_4$ fraction of plasma				
0–25% saturated	+++			
25–35% saturated	++	+++		
33–50% saturated	0		+++	
50% supernatant	0		+++	

In each case the material tested was added to an equal volume of fibrinogen and the mixture clotted by the addition of thrombin. The tubes were incubated at 37° C. and observed for lysis.

0 = No lysis.
+ = Clot present but detached from walls of tube.
++ = Contents fluid but partial clot seen.
+++ = Contents of tube entirely fluid.

On the other hand, when portions of a saline-washed normal whole blood clot were incubated in the patient's serum at 37° C. for up to 48 hours, no lysis of the clot was detected.

A number of experiments were performed in an attempt to characterize the lytic agent further. Samples of the patient's plasma and serum were stored for various intervals of time at different temperatures. Plasma was adsorbed with $BaSO_4$ and $Al(OH)_3$ and fractionated by precipitation with varied concentrations of $(NH_4)_2SO_4$. The material under study was tested by the indirect lysis test. Representative results are summarized in Table 6. Although fibrinolysis was somewhat less active than usual on the occasion of these tests, it was found to be present in all conditions of storage (except in frozen serum, for which observations were incomplete), was not removed by the adsorbing agents, and was present in all of the ammonium sulfate fractions.

After the plasma was separated into electrophoretic fractions by continuous curtain electrophoresis in barbiturate buffer, all of the tubes containing protein material were tested. All produced complete lysis when observed at 16 hours. (Normal plasma, both undiluted and diluted 1:10 in barbiturate buffer, did not show

TABLE 7

Fibrinolytic Effect of Thrombin *

Material Tested (plus added fibrinogen)	Lysis		
	1 Hour	4 Hours	26 Hours
Normal plasma	0	0	0
Imidazole buffer (pH 7.3)	0	Complete	Complete
Barbital buffer (pH 8.6)	0	Complete	Complete
Patient's plasma (stored frozen)	0	0	Complete
Patient's serum (stored frozen)	0	0	Partial

* In each case the contents of the tube were clotted with thrombin, incubated at 37°C., and observed for lysis of the clot.

lysis.) Tests were repeated after concentration of the fractions to approximately one-tenth of the volume. All tubes again showed complete lysis at 18 hours, except for one of four tubes containing the gamma globulin fraction, and the three tubes containing the $alpha_2$ fraction.

Tubes containing fibrinogen and either buffer, patient's plasma or normal plasma were clotted with a small amount of thrombin (10 units in a final volume of 1.1 ml.) and observed for lysis. Results such as those shown in Table 7 were repeatedly obtained.

From this it appears that the patient's fibrinolysis was caused by the absence of an antifibrinolysin normally present in plasma and serum. The inability to isolate, remove by adsorption, or precipitate the fibrinolysin by any of the methods attempted was due to the fact that the "fibrinolysin" was actually the absence of a normal inhibitor, rather than the presence of a normal enzyme or factor.

DISCUSSION

It seems unlikely that the intermittent hemoptysis present for 14 years in this patient was due to the same bleeding tendency discovered later. At the time of his first admission, in 1957, bleeding and clotting times were normal, and a presumptive local site of bleeding was found. When fully developed at the later stages of his illness, the *hemostatic defect* showed the characteristic

multiplicity associated with hepatocellular disease. Although a definite reduction of platelets, prothrombin, proaccelerin, proconvertin, and fibrinogen was noted, none of these was of sufficient degree by itself to produce clinical bleeding. The type of bleeding suggested that the "fibrinolysin" was the decisive factor. Characteristically, there was "rebleeding" after apparently satisfactory hemostasis had occurred, suggesting that in vivo dissolution of clotted blood similar to that observed in vitro was occurring. While the administration of steroids seemed to have a favorable effect on the platelet count and vascular integrity, no effect was noted on the fibrinolytic activity.

Since Goodpasture's original report of fibrinolysis in 1914,[8] many authors have investigated the coagulation defect associated with liver disease.[9-12] Although a distinct increase in fibrinolysis was found to be associated with hepatocellular disease in several systematic investigations,[13-16] cases where the fibrinolysis played a prominent role in the clinical course have been limited in number.[15, 17, 18]

Relatively little is known regarding the mechanism of the fibrinolysis observed. Serafini [19] studied the various components of the fibrinolytic system in nine cirrhotics, and noted reduced levels of plasminogen (profibrinolysin) in both serum and plasma. However, antiplasmin levels were also diminished, and there was an apparent increase in fibrinolysokinase. Hepatectomized dogs show reduced levels of antifibrinolysin.[20] Reduced antifibrinolysin levels are associated with thrombopenia,[21] but the antifibrinolysin found on platelets [22] is probably an adsorption phenomenon, and it seems unlikely that thrombopenia per se plays a causative role.

Contributing to the hemostatic disorder, and presumably related to the liver disease in this patient, were the multiple *vascular abnormalities* noted. The extensive varicosities found in the splenic hilum may have extended during life to the bronchial veins, and rupture of these could have produced the hemoptysis. Spider angiomata and clubbing of the fingers were also prominent. The presence of these numerous vascular abnormalities could conceivably have helped to reduce the number of circulating platelets, due to increased demand. This phenomenon has been observed in infants and children with congenital hemangiomata.[23] No evidence of reduced platelet formation was found in the marrow.

The *anemia* of liver disease has been intensively studied. Even when bleeding is not a significant factor, normocytic or macrocytic anemia is a frequent occurrence. Wintrobe [24] studied 132 cases of various types of liver disease, and noted a macrocytic anemia in 32.6% and normocytic anemia in 30.3%. Hemolytic anemia is frequent.[25] The common association with thrombopenia and leukopenia has suggested a hypersplenic effect to some investigators.[26, 27] Decreased red cell life span has been demonstrated by both the Ashby differential agglutination [28, 29] and the radioactive chromium labeling technics.[27] Splenectomy has had a beneficial effect on the hemolytic anemia in some cases.[25, 30] Steroid therapy has generally been found to be of value when employed.

The hemolytic anemia in our patient was manifested by recurrent episodes of anemia and jaundice, with urobilinogenuria, reticulocytosis, and erythroid hyperplasia in the marrow. There was a good response to steroids, and a relapse followed cessation of therapy. A second good response was also obtained.

The persistent absolute *lymphocytosis* found in our case is exceptional. Usually there are leukopenia and lymphopenia during the acute febrile phase of the hepatitis;[31] later, relative lymphocytosis may occur.[32] In studies of large series of postnecrotic cirrhosis,[1-3] lymphocytosis was not observed.

Disturbed hemoglobin synthesis was manifested by porphobilinogenuria. The increased urinary coproporphyrin excretion noted could have been due to the liver disease or to hemolytic anemia, or to both.

Summary

The case has been presented of a 45-year-old male with postnecrotic hepatic cirrhosis and multiple hematologic abnormalities, including hemolytic anemia, lymphocytosis, thrombopenia, fibrinolysis and other coagulation disturbances, and porphobilinogenuria. The hematologic abnormalities played a prominent part in the clinical symptomatology and overshadowed the cirrhotic picture.

The picture was complex, with multiple abnormalities in the coagulation profile, and absence of a normal inhibitor of fibrinolysis.

The literature pertaining to fibrinolysis and anemia in liver disease is briefly reviewed.

Acknowledgment

The authors wish to acknowledge with gratitude the help of Dr. George Amromin, who performed the post-mortem examination and made his findings available. We are also grateful to Miss Mary Jane Patch for valuable technical assistance, to Mr. Jan Bernat for the figure, and to Mr. Richard Ray for the photographs.

Summario in Interlingua

Es presentate le caso de un masculo de racia blanc de 45 annos de etate con postnecrotic cirrhosis hepatic e multiple anormalitates hematologic—incluse anemia hemolytic, lymphocytosis, thrombocytopenia, fibrinolyse e altere perturbationes del coagulation, e etiam porphobilinogenuria—que habeva un rolo prominente in le symptomatologia clinic e obscurava le tableau cirrhotic. Le curso clinic esseva characterisate per intermittente episodios de jalnessa e sanguination. Plus tarde, septicemia causate per staphylococcos hemolytic superveniva, sed isto respondeva a un therapia antibiotic e steroidic. Tamen, un secunde episodio del mesme genere se terminava letalmente. Le examine necroptic confirmava le diagnose de post-necrotic cirrhosis hepatic.

Investigationes laboratorial revelava thrombocytopenia, un marcate reduction in proaccelerina, e moderate depressiones del nivellos de prothrombina e proconvertina. Le fibrinogeno esseva normal. Le generation de thromboplastina esseva reducite minimemente. Le generation de thrombina esseva marcatemente anormal. Le plus frappante anormalitate esseva le occurrentia de un marcate fibrinolyse. Fractionationes del plasma del patiente per perception con sulfato de ammonium, per absorption con $BaSO_4$ e $Al(OH)_3$, e per electrophorese a cortina non succedeva a isolar le factor fibrinolytic. Per le uso de appropriate tests il esseva demonstrate que iste phenomeno esseva causate per le absentia del normal antifibrinolysina de plasma. Le litteratura relative a fibrinolyse e anemia in morbos hepatic es revistate brevemente.

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LONG SURVIVAL IN DISSEMINATED MYELOMA WITH ONSET AS SOLITARY LESION: TWO CASES *

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We are presenting two cases of myeloma that apparently began as solitary lesions. In both cases, dissemination occurred eventually. It is of interest, however, that we were not able to establish the diagnosis of multiple myeloma in one case on five separate sternal marrow aspirations. These cases are reported because of the initial diagnostic problems and the long survival of the patients.

Case Reports

Case 1. A retired farmer, 63 years old in 1959, was first examined at the Mayo Clinic in 1942. He had no complaints referable to the skeletal system, and the final diagnosis on that admission was angioneurotic edema of unknown cause.

At his next examination at the clinic, which was in 1947, the patient complained of pain in the neck and shoulders. He related the pain to an injury sustained one and one-half years previously. Findings on physical examination were the same as in 1942. Roentgenograms of the thorax and spinal column disclosed only hypertrophic changes in the cervical and thoracic vertebrae, and a small osseous fragment in the region of the coracoid process of the left scapula. Urinalysis and the usual studies of the blood gave negative results. After consultation with an orthopedic surgeon, we decided to pursue a conservative program of management.

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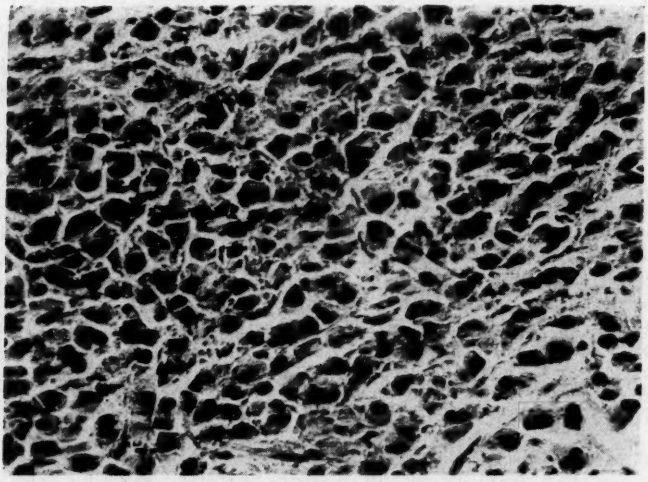

FIG. 1. *Case 1.* Tissue from a thoracic lamina; typical plasma cell myeloma, showing masses of tumor plasma cells (hematoxylin and eosin; × 425).

The patient was admitted for the third time in 1954. He then complained of pain in the thoracic part of the back. He stated that some time after he left the clinic in 1947 the pain had become more marked, and he had consulted another orthopedist, who fitted him with a brace. In August, 1948, he had suffered from acute motor and sensory loss in his lower extremities, for which an emergency thoracic laminectomy had been performed. Slides of tissue obtained at the operation in 1948 were reviewed, and the diagnosis of localized myeloma was affirmed (Figure 1). The patient had been free of pain in the thoracic part of the back from the time of operation in 1948 until 10 days prior to his third admission to the clinic. Physical examination at this time revealed the well-healed surgical incision high in the thoracic region, evidences of previous roentgen therapy to the region, and satisfactory spinal motion. Examination of the cerebrospinal fluid revealed partial block and a level for total protein of 140 mg. per 100 ml. Roentgenograms of the thorax gave evidence of a mediastinal mass, which also was noted in roentgenograms made elsewhere in 1948 (Figure 2). There was no albuminuria, and the blood counts were within normal limits. Elevation of serum globulin was noted (Table 1). The sternal marrow was somewhat hypocellular, but no changes diagnostic of myeloma were seen. Roentgen therapy was given to the involved region of the patient's thoracic vertebrae, with subjective improvement.

The patient returned in 1955 for a routine physical examination. He had no pain, and was asymptomatic. Laboratory data, including findings on sternal aspiration, remained unchanged. The marrow preparation was still hypocellular, but no myeloma cells were seen.

In 1956 the patient was still asymptomatic except for some vertigo. Urine was normal; there was no anemia, and sedimentation rate of erythrocytes, which had been 54 mm. in one hour by the Westergren method in 1955, was 48 mm. The concentration of serum protein had changed, and for the first time the albumin-globulin ratio was reversed (Table 1). Roentgenograms did not show any further diagnostic change.

In June, 1957, the patient returned because of pain in his right shoulder, and anemia. Laboratory data confirmed the anemia, and also disclosed that the sedi-

mentation rate had increased to 105 mm. in one hour, and that there was further hyperglobulinemia (Table 1). Roentgenograms disclosed defects in the midshaft of the right humerus and lateral border of the left scapula, for which roentgen therapy was given.

In December, 1957, the pain had subsided, but roentgenograms disclosed extensive involvement of the ribs by a process consistent with myelomatosis. The patient was subjectively well and had been able to make a long automobile trip in the recent

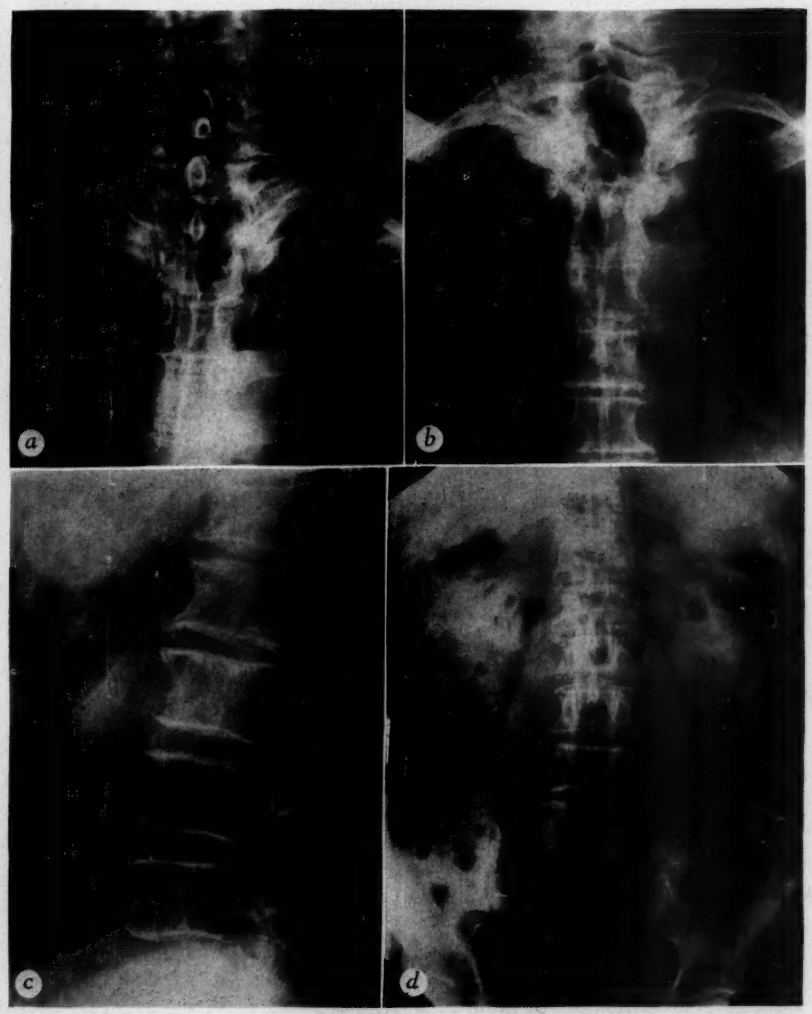

FIG. 2. *Case 1.* (*a*). 1948. A localized lytic lesion of the left part of the body of the second thoracic verebra. (*b*). 1954. It is apparent that the lesion has extended and involves the first and third thoracic vertebrae. (*c*) and (*d*). 1958. Widespread lesions of myeloma, involving the lumbar vertebrae and pelvis.

TABLE 1
Laboratory Data in Case 1

	1942	1947	1954	1955	1956	June 1957	Dec. 1957	1958	1959
Hemoglobin, gm.*	12.7	12.4	12.6	13.0	12.8	11.4	11.2	10.9	10.0
Erythrocytes, millions†			4.21	4.52	4.86	4.43	3.82	3.28	3.96
Leukocytes†	10,000		3,700	3,800	3,400	3,800	4,900	3,000–4,300	4,600
Lymphocytes, per cent					22	18	8.5	21	
Monocytes, per cent					8	16.5	11.0	10	
Polymorphonuclear leukocytes, per cent					61	58.5	75.5	65	
Eosinophils, per cent					9	5.0	4.5	4	
Basophils, per cent						2.0	0.5		
Reticulocytes, per cent							1.0		
Sedimentation rate of erythrocytes, mm. in 1 hr.‡		35	51	54	48	105	120	54	
Smear of peripheral blood			Mild rouleaux	Mild rouleaux	Moderate rouleaux	Moderate rouleaux	Moderate rouleaux	Marked rouleaux	
Platelets†							169,000	188,000–224,000	191,000
Urea, mg.*			36			40	38		
Calcium, mg.*			9.4				9.1		
Phosphorus, mg.*			3.5				3.8		
Total protein, gm.*			7.26	7.69	7.91	7.25	9.75	10.63	
Albumin, gm.*			3.98	4.04	3.55	3.85	3.50	2.49	
Globulin, gm.*			3.28	3.65	4.36	5.40	6.25	7.12	
Urinary albumin, grade	0	1	0		0	2	2	2, 3	
Bence Jones protein							Positive	Positive	

* Per 100 ml. of blood or serum.
† Per cubic millimeter of blood.
‡ Westergren method.

past, during which he had done most of the driving. Sternal aspiration disclosed no changes diagnostic of myeloma.

In December, 1958, the patient returned because of distress in the lumbar region of one month's duration. The previous pain had not recurred. Roentgenograms revealed extensive osteolytic lesions of the ribs, vertebrae, and pelvis (Figures 2*c* and *d*). Again the aspirated sternal marrow did not contain myeloma cells. The patient received roentgen therapy to his lumbar vertebrae. During this period he stumbled and fell against a doorknob, and sustained a compression fracture of the

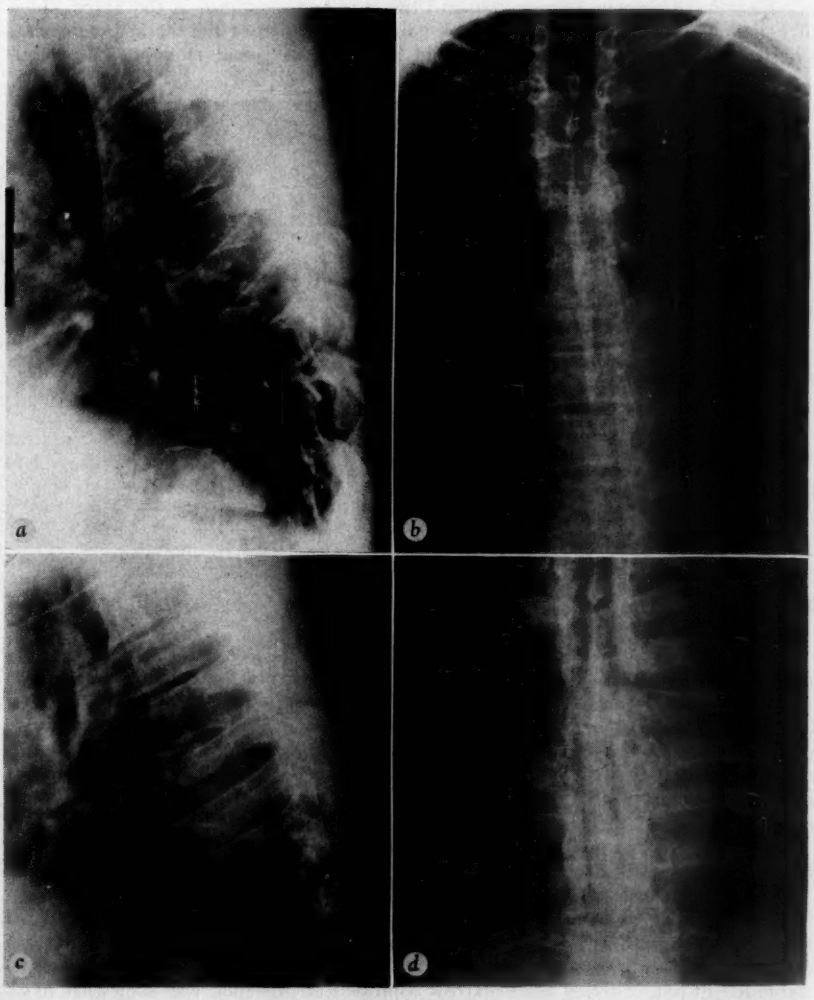

FIG. 3. *Case 2.* (*a*) and (*b*). 1946. Compression fracture of the body of the seventh thoracic vertebra. (*c*) and (*d*). 1953. Soft tissue shadow resembling paravertebral abscess; healed old compression fracture of seventh thoracic vertebra.

second lumbar vertebra. After a short convalescence in the hospital, during which the course of roentgen therapy was completed, he went home feeling well except for moderate lumbar discomfort.

We last saw this patient in March, 1959, when he was complaining of pain low in the back and in the hip. Findings were the same as on previous visits, and the anemia persisted (Table 1). Roentgenograms of the cervical and thoracic vertebrae revealed only hypertrophic and osteoporotic changes. Aspiration of the sternal marrow was studied for myeloma cells again. It was somewhat hypoplastic, but no myeloma cells were seen. Roentgen therapy gave subjective relief of his symptoms.

Case 2. A farmer, 46 years old in 1959, was first examined at the Mayo Clinic in 1946. At that time he complained of pain in the region of the thoracic vertebrae. Physical examination disclosed only mild limitation of spinal motion. Roentgeno-

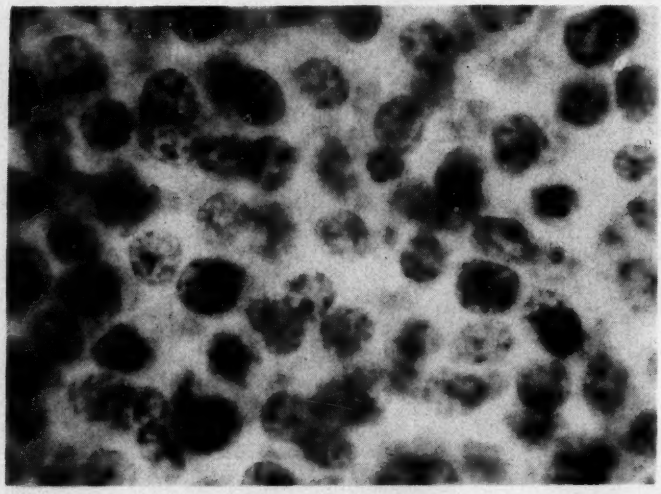

FIG 4. *Case 2.* Tumor from thoracic lamina (hematoxylin and eosin; × 1,500), showing typical myeloma tumor cells.

grams revealed a compression fracture of the body of the seventh thoracic vertebra (Figure 3), but nothing abnormal in the thorax, lumbar vertebrae, or pelvis. After consultation with an orthopedic surgeon, it was decided to pursue a conservative program of management, and the patient was fitted with a Taylor brace. Results of laboratory studies, including tests for Bence Jones proteinuria and examination of sternal-marrow aspirate, were within normal limits. Roentgen therapy was administered.

The patient returned on numerous occasions in 1947. It was noted early that there was no tendency toward healing of the fracture. A study of the sternal marrow failed to reveal any myeloma cells, and there was no apparent explanation for the lack of healing. A bizarre type of collapse following an old compression fracture similar to that in so-called Kümmell's disease was considered to be a possibility. A double bone graft was applied to this region, and subsequent roentgenograms substantiated fusion. Sternal bone marrow aspirated at this time was somewhat hypocellular but did not contain myeloma cells. On examination in 1948 and 1949, the patient stated that his general health was excellent and that he had gained weight.

TABLE 2
Laboratory Data in Case 2

	1946	1947	1953	1956	1958	1959
Hemoglobin, gm.*	15.7	14.0	11.4–13.0	14.3	9.6 –11.2	10.6
Erythrocytes, millions†	4.77	4.88			2.78– 3.93	3.37
Leukocytes†	6,400	4,600	7,000		2,700–6,200	5,400
Lymphocytes, per cent					11.0 –25.5	11.5
Monocytes, per cent					5.5 –13.5	12.0
Polymorphonuclear leukocytes, per cent					63.5 –78.0	73.5
Eosinophils, per cent					1.5 – 8.0	3.0
Basophils, per cent					0.5 – 2.5	
Reticulocytes, per cent						
Sedimentation rate of erythrocytes, mm. in 1 hr.	12 20	20		21–32	87	
Smear of peripheral blood					Mild to moderate rouleaux	
Urea, mg.*			34		70	
Total protein, gm.*	7.71			6.85	7.65	
Albumin, gm.*	4.63			4.29		
Globulin, gm.*	3.08			2.56		
Urinary albumin, grade			2, 3	3		
Bence Jones protein	0			Positive		

* Per 100 ml. of blood or serum.
† Per cubic millimeter of blood.

Roentgenograms revealed destruction of the remainder of the body of the seventh thoracic vertebra.

The patient was next seen at the clinic in 1953. He then complained of recent return of the pain in the area of the involved thoracic vertebrae. He stated, however, that his general health was excellent and that he had no other complaints. Physical

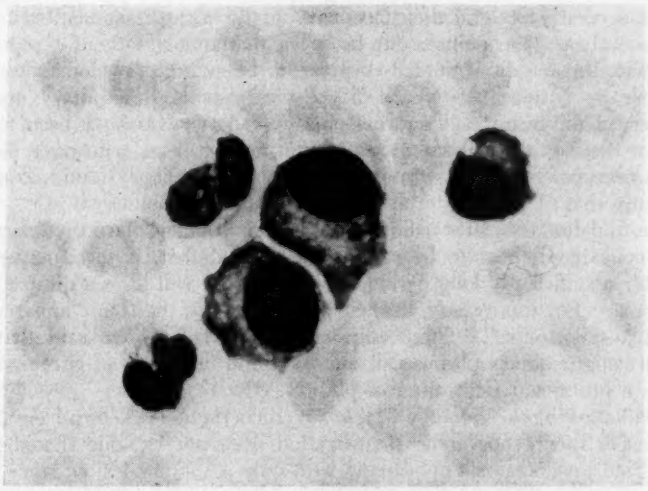

FIG 5. *Case 2.* Smear of sternal marrow, illustrating two myeloma cells and a plasma cell. (The other two cells are myelocytes.) Note the eccentric immature nuclei, prominent nucleoli, and abundant cytoplasm of myeloma cells (hematoxylin and eosin; × 1,300).

examination revealed only the well-healed operative scar over the thoracic vertebrae. Urinalysis revealed pyuria, microhematuria of grade 1 (on a grading basis of 1 to 4), and albuminuria. Roentgenograms displayed a paravertebral mass extending from the fifth to the ninth thoracic vertebra. A diagnosis of tuberculosis was entertained (Figure 3), but tests with single and second strength tuberculin, as well as agglutination tests for typhoid, paratyphoid, and Brucella, gave negative results. Costotransversectomy was done. Tissue removed from the seventh and eighth thoracic vertebrae revealed plasma cell myeloma (Figure 4). Sternal bone marrow aspirated at this time revealed active myelopoiesis and background of rouleaux, but no myeloma cells were seen. Roentgen therapy gave relief of the pain.

Results of physical and laboratory examinations in 1953, 1954, and 1955 were essentially the same. In 1956, Bence Jones proteinuria was noted for the first time.

When the patient returned in 1958 he related that he had been in good health except for two episodes of pneumonitis in 1957. He was anemic and azotemic, and had a significantly higher sedimentation rate of erythrocytes (Table 2). Roentgenograms revealed osteolytic areas of destruction throughout the lumbar vertebrae and pelvis consistent with a diagnosis of multiple myeloma. The sternal marrow obtained by aspiration revealed myeloma cells which were relatively mature (Figure 5). Chemotherapy consisting of three doses a day of 0.5 gm. of urethane and 2 mg. of chlorambucil (Leukeran) was begun. Leukeran therapy was discontinued after six months, but the patient continued to take the urethane.

The patient was re-examined frequently in 1958 and again early in 1959, at which time his condition was essentially unchanged except for slight hepatomegaly in 1959. He had remained asymptomatic, and was still able to work actively when last seen in April, 1959.

Comment

Classification: Several workers who have been interested in studying myelomas have had varying experiences with the solitary plasma cell tumors of bone. Christopherson and Miller [1] acknowledged that solitary myelomas may seem benign for several years and then terminate fatally with dissemination in a few weeks or months. They pointed out, however, that almost without exception the lesions which become disseminated or prove to be multiple myelomas are manifested clinically within three years of the diagnosis of the solitary myeloma. They reserved the term "solitary myeloma" for those who have been followed for at least three years without dissemination, or for those who have died and for whom necropsy has disclosed only a solitary lesion. They found 25 cases in the literature that fit these criteria.

Carson and his associates [2] did not deny that solitary plasmacytomas exist, but they considered them to be rare. They stated that, if these patients are followed for a sufficiently long period, they eventually will have a diffuse plasma cell myeloma. For this reason, in their paper they use the term "apparent solitary plasma cell tumor." These authors and others [3, 4] have said that some seemingly benign solitary plasma cell tumors are in fact areas of chronic inflammation with prominent infiltration of plasma cells.

Dissemination of the Solitary Myeloma: Bichel and Kirketerp [5] emphasized that extensive roentgenographic investigation does not exclude the possibility of generalized myelomatosis in patients with only a solitary lesion, since sternal aspiration in two of their cases revealed myeloma cells. Other roentgenologists [6, 7] have reviewed the subject of solitary myeloma of bone.

Length of Survival: Bayrd,[8, 9] in reviewing the medical literature, found six

reports of myeloma with multiple lesions where the patients survived beyond the seventh year. Kenny and Moloney [10] noted that such patients had in common a small population of myeloma cells in the bone marrow, and that these cells were of the mature type. Also, their patients had only minimal urinary, hematologic, and osseous disturbances.

Weiner [11] found that the myeloma in only four of 563 (0.7%) proved cases of myeloma studied at the Mayo Clinic remained solitary for more than nine years. He noted, however, that survival appeared to be longer among patients who presented with a solitary lesion and who later manifested dissemination of the myeloma than it did among patients who presented with the characteristic picture of multiple myeloma.

In his review of 563 cases of myeloma diagnosed histologically at the Mayo Clinic from 1905 through 1955, Weiner referred to 60 cases that were called cases of solitary myeloma. In these cases, lesions were considered to be solitary if roentgenograms revealed only a single skeletal lesion which on biopsy proved to be myeloma, and if the findings on sternal aspiration were not characteristic of multiple myeloma. Follow-up data on 45 of these patients were satisfactory. In 16 the myeloma remained solitary for from 2.3 to 16 years, and in 29 it became disseminated and the diagnosis then was considered to be multiple myeloma. No histologic differences were demonstrated between the persistently solitary lesions and those becoming disseminated.

Summary

Two cases of localized myeloma with later dissemination are reported. The patients have survived 11 and 13 years, respectively, after the onset of symptoms. The first patient's lesion apparently remained solitary for approximately nine years after the histologic diagnosis was established before the first signs of dissemination became apparent. The second patient was first seen with a lesion of the seventh thoracic vertebra. The histologic diagnosis of this lesion was not established for approximately seven years after the appearance of the lesion, and then it involved both the seventh and the eighth thoracic vertebrae. Ten years elapsed between the recognition of a lesion of the seventh thoracic vertebra and the appearance of the first systemic reaction indicated by Bence Jones proteinuria, and 12 years from the observation of the initial osseous lesion to the finding of dissemination of bony lesions.

These cases emphasize again the need for a guarded prognosis in any solitary osseous lesion which has the characteristics of a plasma cell myeloma.

Summario in Interlingua

Es reportate duo casos de myeloma localisate con dissemination subsequente. Le patientes ha supervivite 11 e 13 annos, respectivemente, depost le declaration del symptomas. In le caso del prime patiente, le lesion pare haber remanite solitari durante approximativemente novem annos a partir del establimento del diagnose per medios histologic ante que le prime signos de dissemination se faceva manifeste. Le secunde patiente esseva primo vidite con un lesion del septime vertebra thoracic. Le diagnose histologic de iste lesion non esseva establite usque approximativemente septe annos post su apparition, e alora illo interessava tanto le septime como etiam le octave vertebra thoracic. Dece annos passava inter le recognition de un lesion del septime vertebra thoracic e le apparition del prime reaction systemic manifeste

in proteinuria de Bence Jones; e 12 annos passava inter le observation del lesion ossee initial e le constatation de disseminate lesiones ossee.

Iste casos signala de novo le necessitate de prognosticar con circumspection in casos de solitari lesiones ossee que ha le characteristicas de myeloma plasmocytic.

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APPARENT REMISSION OF A SEVERE DIABETIC ON DEVELOPING THE KIMMELSTIEL-WILSON SYNDROME * †

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The amelioration of diabetes in some patients upon the development of the Kimmelstiel-Wilson syndrome has been well documented.[1] That this is not specific for the Kimmelstiel-Wilson lesion alone but is more characteristically seen in diabetics who develop a wide variety of renal lesions has also been commented upon.[2] This is a report of an interesting and unusual patient with

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severe diabetes of 15 years' duration who went into an apparently complete remission on developing the clinical picture of diabetic glomerulosclerosis.

Case Report

A 52-year-old Negro female was admitted to District of Columbia General Hospital for the first time in 1948 for regulation of her diabetes mellitus. She had been a known diabetic for 10 years, and had been receiving insulin for the last eight years. She had had one hospitalization for hyperglycemia at another hospital five years previously, and had been admitted in a "near coma" state. Since then she had been followed in the diabetic clinic, which she attended irregularly. Her blood glucose levels were in the range of 200 to 300-plus mg. per 100 ml., and she consistently had 3 to 4-plus glycosuria. At the time of her 1948 admission she was taking 60 units of protamine zinc insulin and 30 units of regular insulin. There was no known family history of diabetes. Her blood pressure was 132/84 mm. Hg, and her weight was 133 pounds. At the onset of her diabetes, in 1938, her weight had been 161 pounds, and she had lost approximately 30 pounds over the ensuing years until the time of this admission. She had noticed a gradual decrease in her vision, especially on the right, and bilateral lenticular opacities were noted on physical examination. Laboratory examination revealed 4-plus glycosuria and a fasting blood sugar of 284 mg. per 100 ml. Her diabetes was controlled and she was discharged on a diabetic diet, 65 units of protamine zinc insulin before breakfast, and 35 units of regular insulin before lunch. Her fasting blood sugar at the time of discharge was 167 mg. per 100 ml.

The patient was followed in the diabetic clinic at fairly regular intervals but refused to adhere to her diet. She usually had 3 to 4-plus glycosuria, and fasting blood sugar levels were 200 to 300 mg. per 100 ml. Her insulin dosages varied widely, for she insisted on regulating the dosage herself, depending upon how she felt. She was fairly insulin-resistant, never going into acidosis, and rarely having insulin reactions at this point. In 1949, diabetic retinopathy was noted, with marked sclerosis of the vessels, microaneurysms, scattered small deep and superficial hemorrhages, and an occasional cotton-wool exudate. For the first time, 2-plus proteinuria was seen, and the blood pressure was recorded as 170/100 mm. Hg.

In 1951 the patient was readmitted to the hospital with acute glaucoma. Her blood pressure was 160/90 mm. Hg; fasting blood sugar, 114 mg. per 100 ml. Numerous specimens of urine were negative for sugar and acetone, but there was a trace of protein. She was treated medically, and the glaucoma showed improvement. For the first time her diabetes showed marked clinical improvement. Her final fasting blood sugar was 162 mg. per 100 ml., without glycosuria. She was discharged on a diabetic diet and 20 units of protamine zinc insulin.

The patient was followed in the outpatient department over the next one and one-half years. The blood sugar level averaged 200 mg. per 100 ml., with a range of 138 to 316 mg. per 100 ml. She gradually developed signs and symptoms of congestive heart failure in the summer of 1952 and was digitalized. From this point until her death, the fasting blood sugar was rarely recorded above 120 mg. per 100 ml. In November, 1952, it became increasingly difficult to control the congestive heart failure, and she was rehospitalized. At that time she was taking 40 units of protamine zinc insulin daily. She was complaining of dyspnea, orthopnea, dull pain in the right chest, and chronic cough. Physical examination revealed a blood pressure of 184/108 mm. Hg, and a weight of 142 pounds. She was totally blind, due to cataract formation. Bilateral râles were heard in the bases posteriorly, and the heart was enlarged to the anterior axillary line. The liver was four fingerbreadths below the right costal margin and tender to palpation. There was 2-plus pitting

edema of the lower extremities up to the knees. Laboratory examination revealed a fasting blood sugar of 88 mg. per 100 ml. Subsequent blood sugar tests were 70 and 94 mg. per 100 ml. The urine revealed 4-plus proteinuria, no glycosuria, and a phenolsulfonphthalein excretion of 23% in 20 minutes. The blood urea nitrogen was 28 mg. per 100 ml.; total protein, 6 gm. per 100 ml., with albumin, 3.5 gm. per 100 ml., and globulin, 2.5 gm. per 100 ml. X-ray examination of the chest revealed cardiac enlargement and pulmonary congestion. An electrocardiogram was interpreted as showing a left ventricular strain pattern. The patient's insulin requirements decreased from 40 units of protamine zinc insulin to zero. The urine remained sugar-free, and her fasting blood sugar was within normal limits. Kimmelstiel-Wilson syndrome was first suspected at this time.

The patient's course over the next year remained essentially unchanged. She was given insulin intermittently, but most of the time her blood sugar was within normal limits. In January, 1954, at the age of 58, she was readmitted to District of Columbia General Hospital because of congestive heart failure. At this time she

TABLE 1

Glucose Tolerance Test

4/29/54				5/17/54			
Time	Blood Sugar mg./100 ml.	Urine		Time	Blood Sugar mg./100 ml.	Urine	
		Sugar	Acetone			Sugar	Acetone
Fasting	96	Negative	Negative	Fasting	66	Negative	Negative
30 minutes	140	Negative	Negative	1 hour	140	Negative	Negative
1 hour	140	Negative	Negative	2 hours	125	Negative	Negative
2 hours	183	Negative	Negative	3 hours	108	Negative	Negative
3 hours	203	Negative	Negative				

was taking 30 units of protamine zinc insulin daily. Her blood pressure was 120/80 mm. Hg; fasting blood sugar, 112 mg. per 100 ml.; blood urea nitrogen, 37 mg. per 100 ml. Three-plus proteinuria was present, but a urine culture was sterile. The patient was treated with digitalis, mercurials, and ammonium chloride. Her insulin requirement during this period of stress decreased, and her fasting blood sugar was 69 and 66 mg. per 100 ml. on two separate occasions. She was discharged on 20 units of protamine zinc insulin daily.

After the patient left the hospital her condition again deteriorated, and she had to be readmitted eight weeks later because of congestive heart failure. On admission she was taking 30 units of protamine zinc insulin daily. Her blood pressure was 130/80 mm. Hg, and her weight was 137 pounds. A fasting blood sugar was 162 mg. per 100 ml., and the urine was negative for sugar and acetone. Several days later she developed symptoms of hypoglycemia and the insulin was stopped. Fasting blood sugar determination after stopping insulin remained below 120 mg. per 100 ml. Sugar and acetone continued to be absent from the urine, but proteinuria (1 to 2-plus) persisted. The blood urea nitrogen ranged from 32 mg. per 100 ml. on admission to 40 mg. per 100 ml. on discharge. She was discharged without insulin therapy on April 13, 1954, to be followed in the outpatient department. Subsequent fasting blood sugars were 90 and 123 mg. per 100 ml., without glycosuria. On April 29, 1954, a three-hour glucose tolerance test after stimulation with 100 gm. of glucose was performed (Table 1).

On May 17, 1954, the patient was admitted to the hospital, in congestive heart failure with pneumonitis. Her blood pressure was 142/90 mm. Hg; fasting blood

sugar, 83 mg. per 100 ml.; blood urea nitrogen, 36 mg. per 100 ml.; proteinuria, 4-plus. She responded well to antibiotics and diuretics. A repeat glucose tolerance test after 100 gm. of glucose was normal (Table 1).

On May 27, 1954, a renal biopsy showed severe diabetic glomerulosclerosis (Figure 1). Inulin clearance was 33 ml./min.; maximal tubular excretory capacity for para-amino-hippuric acid, 33 mg./min.; urea clearance, 17 ml./min.

The patient was discharged after one month to be followed in the outpatient department. During the next 10 months she had three other admissions to District of Columbia General Hospital for bouts of congestive heart failure. During this time she had repeated blood sugar determinations, both in the hospital and in the outpatient department, all of which were below 120 mg. per 100 ml. Her urines remained sugar-free, and she received no insulin after April, 1954. She was last discharged from the hospital on April 16, 1955, and died suddenly at home a few days later. An autopsy was not obtained.

FIG. 1. Renal biopsy, showing the typical changes of diabetic glomerulosclerosis. × 300.

DISCUSSION

While it has been clinically recognized for many years that the progression of renal disease in diabetics in general, and of the Kimmelstiel-Wilson lesion in particular, has been associated with the apparent decreased severity of the diabetes as manifested by a decrease in the insulin requirement, only within recent years has this phenomenon been properly evaluated. Zubrod et al.[1] found that diabetes in the patients with Kimmelstiel-Wilson disease was just as severe during the midphase of the disease as was that of controls. It was not until the preterminal period that an insulin requirement of 20 units or less was found in 83% of the Kimmelstiel-Wilson patients, as opposed to 28% of those with other renal lesions, and to 22% of those without renal lesions. It was also noted that 16% of the Kimmelstiel-Wilson patients had preterminal blood glucose concentrations below 80 mg. per 100 ml., and 46% were below 120 mg. per

100 ml. On the other hand, Runyan et al.[2] found only a slight decrease (2 units) in the average insulin requirement from the midphase to the preterminal period in both those with and those without the Kimmelstiel-Wilson lesion. They also found an increase in the insulin requirement in 27.8% of the Kimmelstiel-Wilson patients, and in 25% of the group without the lesions. The two groups were very similar in the proportion of patients with increases and decreases in insulin requirement. There was a reduction of the insulin requirement in most of the cases with the clinical syndrome seen in Kimmelstiel-Wilson disease, and the syndrome was most common in the patients with the Kimmelstiel-Wilson lesions in the kidney. Only five of 138 patients with proved Kimmelstiel-Wilson lesions required no insulin before the terminal admission, and only three needed no insulin for one year or longer. That the case reported here fits into this small category is evidenced by the fact that during the midphase of the patient's diabetes, while in periods free of stress, she frequently required up to 100 units of insulin daily. The insulin requirement began to decrease in late 1951, shortly before the appearance of the clinical picture of Kimmelstiel-Wilson disease (edema, proteinuria, hypertension). (The proteinuria and hypertension had been noted two years earlier, but the edema did not appear until 1952, with the onset of congestive heart failure.) This is in keeping with the findings of Wilson et al.,[3] who noted a decrease in insulin requirement with the onset and progression of renal insufficiency, cardiac decompensation, and blindness. The patient's need for insulin first disappeared completely in 1952, and from then until the time of her death, a full three years later, she received insulin only intermittently. In 1954, when the Kimmelstiel-Wilson lesion was proved by renal biopsy, she developed symptoms of acute hypoglycemia after receiving 30 units of protamine zinc insulin, and did not receive insulin again in the remaining year of her life. In like manner, her blood glucose levels, which until 1951 had consistently risen to the 200 to 300 mg. per 100 ml. range, subsequently rarely rose above 120 mg. per 100 ml., even without insulin.

It is interesting to note that, while the patient had an abnormal glucose tolerance test in 1954, a repeated glucose tolerance test, taken during hospitalization three weeks later, was within normal limits. One would like to cite this as further proof of remission of the diabetes, along with the persistently normal blood glucose levels even during periods of stress. Unfortunately, the glucose tolerance test was not repeated for confirmatory evidence.

Amelioration of the severity of the diabetes with the development of the Kimmelstiel-Wilson lesion has been postulated by some [1] to represent a specific type of diabetes. This has been refuted by Runyan et al.,[2] Epstein and Zupa,[4] Rifkin,[5] and others who have noted similar findings in diabetics with a wide variety of nonspecific renal disease. Indeed, intercapillary glomerulosclerosis in diabetic patients seldom occurs as the only renal lesion seen on biopsy or at post-mortem examination. That the renal involvement is almost invariably of mixed etiology, including both degenerative and infectious elements, has been commented on by Wilson and his group.[3] They have suggested use of the term "diabetic nephropathy" as more descriptive of these patients than is "diabetic glomerulosclerosis" alone.

The most likely explanation of the improvement in the diabetic state seems to be concerned with a prolonged decrease in caloric intake, brought on by the

anorexia and/or the distasteful low salt diet which accompanies the onset of renal or congestive failure, and which is not manifested by weight loss in the presence of the usual edematous state. This, plus the elevated threshold for glucose in the kidney, probably makes the improvement in the diabetic state more apparent than real.

Summary

A patient with severe diabetes for more than 14 years gradually improved with the advent of early manifestations of the Kimmelstiel-Wilson lesion, and progressed to an apparently complete remission of more than one year's duration with the onset of the fully developed clinical syndrome of edema, proteinuria, and hypertension.

Summario in Interlingua

Le observation clinic que patientes diabetic pote exhibir marcate grados de melioration in le severitate de lor diabete post le declaration de morbo renal es ben cognoscite. Glomerulosclerosis diabetic in particular pote esser associate con le melioration de diabete, manifeste in le reducite requirimento de insulina. Es reportate le caso de un patiente con sever diabete de multe annos de duration qui requireva usque a 100 unitates de insulina per die pro le stabilisation de su condition. Dece-tres annos post le declaration del diabete, le tableau clinic del syndrome Kimmelstiel-Wilson (edema, proteinuria, hypertension) se disveloppava. A iste tempore, le requirimento de insulina comenciava declinar e dispareva completemente un anno plus tarde. In le curso del sequente tres annos, illa requireva insulina a infrequente intervallos solmente, e isto in despecto de periodos de stress (congestive disfallimento cardiac) e de infection (pneumonitis). Illa esseva completemente independente de insulina durante le ultime anno de su vita, con nivellos de glucosa de sanguine—previemente in le region inter 200 e 300 mg per 100 ml—montante rarmente in supra de 120 mg per 100 ml post le declaration del syndrome Kimmelstiel-Wilson. Un biopsia renal confirmava le diagnose clinic de glomerulosclerosis diabetic. Le possibilitate que le lesion de Kimmelstiel-Wilson representava un specific typo de diabete es pauco probabile, proque simile meliorationes del stato diabetic ha essite notate in un varietate de non-specific morbos renal. Un plus plausibile explication poterea esser vidite in le prolongate reduction del ingestion caloric (un corollario commun de progressive morbo renal) in conjunction con un elevate limine tubular pro glucosa. Si isto es correcte, le melioration del stato diabetic in tal casos esserea plus apparente que real.

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HEMOCHROMATOSIS AND HEART FAILURE: PRESENTATION OF A CASE WITH SURVIVAL AFTER THREE YEARS' TREATMENT BY REPEATED VENESECTION *

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INTRODUCTION

SINCE Trousseau [1] first described hemochromatosis, much has been written about the disease, as to both its pathology and its possible causation. In the classic monograph by Sheldon,[2] myocardial failure is mentioned as an infrequent cause of death in hemochromatosis.

With the advent of the use of insulin, diabetes has ceased to be the prime cause of death in hemochromatosis, and has been replaced by hepatic and cardiac failure.

The reports which have appeared in recent years dealing with the heart in hemochromatosis have all stressed the fact that, once failure has manifested itself, deterioration is rapid, with survival usually not exceeding one year.[3-9] The case reported here presents the unusual feature of a patient's survival in a state of continuing good health three years after onset of failure, and whose hemochromatosis responded dramatically to a plan of repeated venesection employed over the same period of time.

CASE REPORT

A 45-year-old farmer was admitted to the Veterans Administration Hospital, Oakland, California, on December 11, 1956, with the chief complaints of shortness of breath, orthopnea, and leg edema. He had been well until four years prior to entry, when he developed symptoms of polyuria, polyphagia, and polydipsia. After sustaining a weight loss of 30 pounds, he sought medical help in September, 1956. A diagnosis of diabetes mellitus was made at that time. On a program of dietary management and lente insulin his diabetes was well controlled and he did well until one week prior to admission, when he developed his cardiac complaints. The patient's past history was noncontributory.

The pertinent physical findings on admission were: weight, 161 pounds; temperature, 98.6° F.; pulse, 80; respiration, 18. The skin presented a bronzed appearance, and was smooth and devoid of hair. The axillae were also free of hair. The escutcheon was female in type. The neck veins were distended in the semirecumbent position. The left border of cardiac dullness extended to the anterior axillary line, at the fifth interspace. The rhythm was regular, and no murmurs were audible. Blood pressure was 92/76 mm. Hg. The lungs were clear except for suppression of breath sounds at the bases. The liver edge was felt four fingerbreadths below the right costal margin and was slightly tender. A hepatojugular reflux was present. An abdominal fluid wave was felt. There were edema of the abdominal wall and 4-plus edema of the legs. The testes were small and atrophic.

Laboratory Data: Urinalysis was within normal limits. Hematocrit, 44%; white blood cell count, 4,800/cu. mm., with a normal differential. Platelet count 196,800/cu. mm. Blood serologic test for syphilis, negative. Blood urea nitrogen, 22 mg.%.

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Serum proteins, 6.3 gm.%, with 4.2 gm. of albumin and 2.1 gm. of globulin. Serum bilirubin, 4.1 mg.%; thymol turbidity, 3 units; cephalin cholesterol flocculation, 3-plus in 48 hours. Serum total cholesterol, 167 mg.%. Serum potassium, chloride, and CO_2-combining power, within normal limits. Basal metabolic rate, plus 7%; protein-bound iodine, 5.7 μg.; 17-ketosteroid determination, 7.1 mg. in a 24-hour urine specimen. Fasting blood sugar, 64 mg.%; two-hour postprandial blood sugar, 618 mg.%. Prothrombin time, 73% of normal concentration. Arm-to-tongue circulation time with Decholin, 35 sec. Venous pressure, 33 cm. of saline. X-ray of the chest (Figure 1) revealed the heart to be grossly enlarged, with a maximal transverse

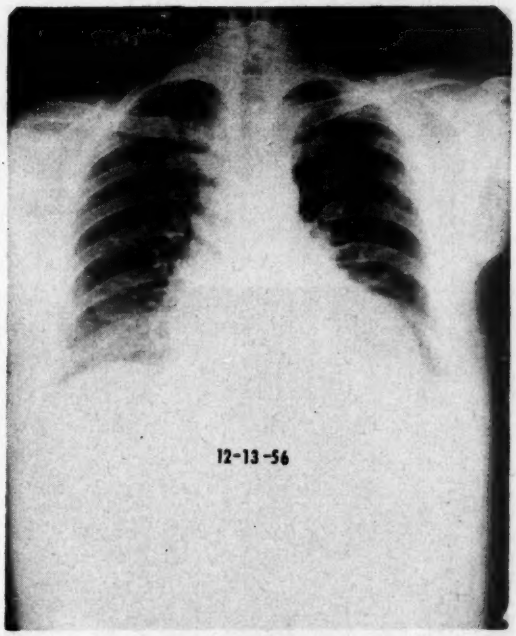
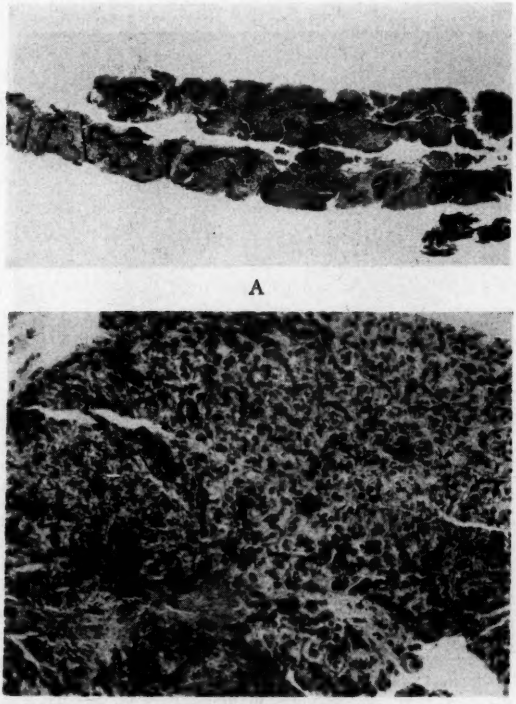


FIG. 1. X-ray of chest, showing grossly enlarged heart, with moderate congestive changes in lungs.

diameter of 17.5 cm. There were moderate congestive changes in both lung fields. An electrocardiogram showed the QRS complexes to be of low voltage; there was clockwise rotation, with inverted T waves in V-1 through V-5. Histologic examination of a liver biopsy specimen showed marked proliferation of fibrous tissue in the portal area, the latter being infiltrated with lymphocytes and plasma cells. There was marked deposition of golden brown pigment within the hepatic cells, and even within the epithelial cells of the bile ducts. The pigment stained bright blue with Prussian blue. Diagnosis: hemochromatosis of the liver, with associated cirrhosis (Figures 2A, 2B).

Course and Treatment: The patient was digitalized. One injection of Mercuhydrin was administered during the first week of his hospital stay. He was also given 20 units of NPH insulin daily, and a 2,000-calorie diet. Five phlebotomies were performed during this period of hospitalization, and a total of 2,250 ml. of blood, equivalent to 1.125 gm. of iron, was removed. During the first week of his hospital

stay he sustained a weight loss of 20 pounds after a sizable diuresis. Following this weight loss he became symptom-free. A repeat chest x-ray (February 21, 1957) revealed a decrease of the transverse diameter of the heart to 16 cm., and clearing of the pulmonary congestive changes. Repeat electrocardiograms showed no change from the one taken on admission. Repeat hemoglobin and red blood cell determinations (February 20, 1957) were 13.6 gm. and 4,600,000, respectively. The patient was discharged on a maintenance dose of 1½ gr. of digitalis leaf daily, 20 units of NPH insulin, and a 2,000-calorie diet.



A

B

FIG. 2. (A). Photomicrograph × 14 of liver biopsy, showing cirrhotic changes and marked hemosiderin deposition. (B). Photomicrograph × 120. Liver biopsy, 12/13/56, showing marked hemosiderin deposition.

The patient was readmitted on June 21, 1958, for re-evaluation and liver biopsy. In the interim he had undergone 73 venesections of 500 ml. each. His hemoglobin concentration had thus been maintained at slightly anemic levels. On this program he experienced no symptoms of heart failure, despite strenuous activity as a farmer. His digitalis was discontinued on December 19, 1957, one year after his initial admission. By July, 1957, his liver could no longer be palpated. Repeat chest x-rays between discharge and readmission showed no change.

Physical examination at time of re-entry showed the patient's weight to be 138 pounds. His skin seemed to be less bronzed. Blood pressure was 130/80 mm. Hg. The cardiovascular system showed no abnormalities. The liver edge was felt 1 to

1½ cm. below the costal margin on deep inspiration. There was no change in the quantity or distribution of body hair. The laboratory findings were: hemoglobin, 14.5 gm.; urinalysis: specific gravity, 1.030; protein, slight trace; sugar, 3-plus. Prothrombin time, 85% of normal. Serum proteins, 6.7 gm.%; albumin, 4.7 gm.%. Cephalin cholesterol flocculation, negative in 48 hours. X-rays of the heart and lungs were within normal limits. Liver biopsy now revealed a marked decrease in iron deposits, to an estimated one-third of the amount present on the first biopsy (Figures 3A, 3B). The patient was discharged on a 2,800-calorie diet and 40 units

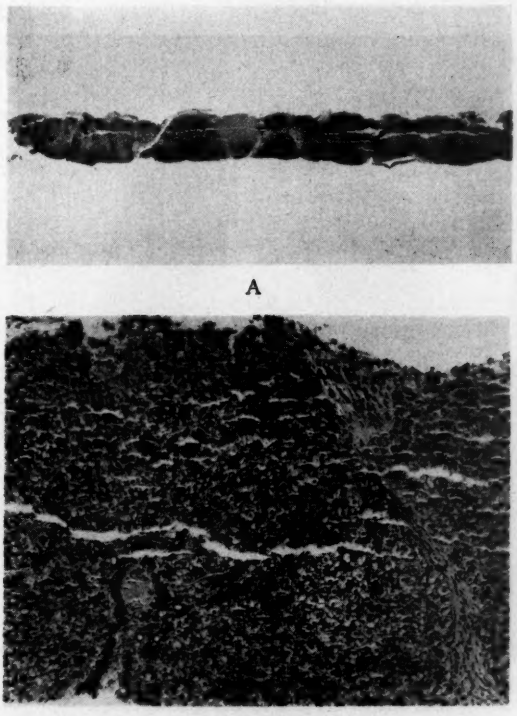


FIG. 3. (A). 6/21/58. Photomicrograph × 14. Liver biopsy. Marked fibrosis. Marked diminution in quantity of hemosiderin. (B). 6/21/58. Photomicrograph × 120. Liver biopsy. Marked diminution in amount of hemosiderin.

of NPH insulin. He was to return for weekly phlebotomies. Between June 12, 1958, and October 22, 1959, a total of 52 phlebotomies was performed, with withdrawal of 500 ml. of blood each time. The patient was thus maintained in a slightly anemic state. In all, the patient underwent 125 phlebotomies, with removal of 62,500 ml. of blood, or 31.25 gm. of iron.

Repeat chest x-ray on October 22, 1959 (Figure 4), showed the lungs and heart to be within normal limits, with no change since the last x-ray. Repeat electrocardiogram on the same date remained unchanged from those taken on prior occasions.

Discussion

This patient's cardiac symptoms became manifest four years after the onset of his diabetes mellitus. It is reasonable to assume that the latter represented the first evidence of hemochromatosis. Schreiber [3] cites Keshner's statement that, with the advent of insulin therapy for diabetes, hepatic and heart failure has superseded diabetes as the principal cause of death in hemochromatosis. The use of insulin enabled our patient to survive long enough to develop myocardial decompensation.

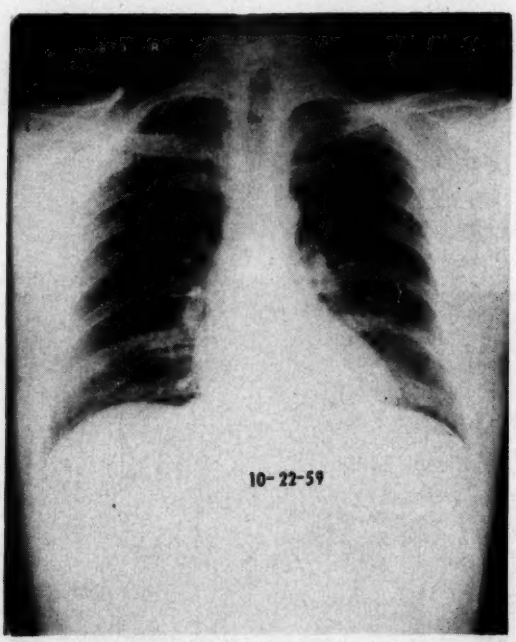


Fig. 4. 10/22/59. Repeat chest x-ray, showing return of heart size to normal and clearing of congestive changes in lungs.

Reports by Petit,[10] Tucker et al.,[5] Horns,[9] Lewis,[4] and Littman et al.[7] stress the predominantly right-sided aspects of failure in this disease, an event one might expect from a process which involves the entire myocardium. Our patient, too, presented a picture of predominant right-sided congestive failure. The engorgement of the neck veins, the comparatively slight degree of pulmonary congestion, the tender liver and positive hepatojugular reflux, the ascites, the abdominal wall and leg edema, and the elevated venous pressure all point in this direction.

The ST-T wave changes and the low voltage of the QRS segment are nonspecific in nature, standing as they do for myocardial disease of plural etiology. They have been described by others.[3, 8, 11] The tendency to the development of arrhythmias and various types of heart block is frequently mentioned. This

patient's electrocardiogram remained stationary throughout the three years of observation and after 31.25 gm. of iron had been removed. Schreiber's [3] and Kleckner's [11] cases survived only a short time, and one might ascribe the absence of electrocardiographic reversal to the brief period of survival. In the series of six cases reported by McAllen et al.,[8] only one had heart failure. In that case, too, the abnormal electrocardiographic pattern persisted in spite of repeated phlebotomies over a two-year period. It would seem illogical to incriminate hemosiderin in the myocardium as the cause for the persistence of the abnormal electrocardiographic patterns, for one would expect evidence of improvement with hemosiderin removal.

In a review of the literature of hemochromatosis, Bothwell and Alper [13] tabulated 33 cases with heart failure. Their conclusion is that, once heart failure ensues, death follows within a period of one year. Our patient's course did not fulfill this statistical augury. He continues to survive, usefully engaged in arduous physical activity, three years after onset of failure.

McAllen et al.[8] believe that their patient, who continued free of failure after two years on a regimen of repeated venesections, represents the first such instance. Our case would seem to be the second such occurrnce following repeated phlebotomies.

It will be recalled that, during his first week of hospitalization, our patient sustained a weight loss of 20 pounds before the institution of phlebotomy. At this point he felt greatly improved. During his initial hospital stay, a total of 1.125 gm. of iron was removed. These facts do not offer convincing proof that the patient's rapid recovery can be attributed to the four phlebotomies.

As far back as 1935, Sheldon [2] conjectured that, although hemochromatosis was a disease manifesting itself pathologically by iron, hemofuscin, and melanin deposition in tissues, such deposition was not the primary cause for the cirrhotic changes observed, but rather was secondary to a metabolic disturbance in the cells involved. This attitude has been popular in the French literature, and only recently has it acquired wider acceptance in this country.

Certain clinical, experimental, and pathologic data tend to support the "metabolic-causation" theory. Higginson et al.[14] and Gillman and Gillman [15] have found that, even though siderosis is common in the Bantus, hemochromatosis is not. Clough [12] has stated that in "hemochromatosis there is no close correlation between the amount of hemosiderin in a tissue and the degree of fibrosis. In certain tissues such as the chief cells of the stomach, the cells may be regularly stuffed with granules, yet show no detectable anatomic or functional alteration." The same view is shared by Kleckner et al.[11] Brown et al.,[16] in experiments on dogs, failed to reproduce hemochromatosis utilizing doses of iron sufficient to produce tissue concentrations equal to those found in affected humans and administered over equivalent periods of time. Massive transfusions have also failed to produce hemochromatosis. In those in whom the disease does develop after transfusions, it is by no means certain to what extent the responsibility lies with the underlying disease for which blood is given.[24] According to Golberg,[17] the extensive use of parenteral iron on a global scale has failed to produce one case of siderosis in the last 10 years.

Some other factor—such as species difference, for example—may be responsible for the production of the disease in human beings. Uzman et al.[18] believe

that in Wilson's disease there is a defect in protein metabolism in which abnormal tissue proteolytic activity leads to protein or polypeptide residues with high affinity for copper. A parallel situation may obtain in hemochromatosis, i.e., a metabolic defect aggravated secondarily by iron deposition. The use of repeated venesection in the treatment of this disease, as first practiced by Davis,[19] may be attacking the last link of the pathologic chain.

Sufficient reversibility of the cardiac disease process may have existed in our patient upon admission to allow for good response to routine cardiac therapy. Insofar as the amount of iron in the myocardial fibers is no guide to the degree of myocardial functional impairment, it may be fair to assume that the amount of iron withdrawn may not reflect proportionately the amelioration induced. It is possible that the myocardium may require less iron depletion for improvement than do other organs per period of time, and therefore, that even the small amounts of iron recovered during the first period of hospitalization may have contributed in some measure to his rapid recovery.

The sustained recovery may be attributed to the removal of *31.25 gm. of iron over a period of three years.* An indication of such improvement can be gained from a comparison of the two liver biopsies, the first taken at the time of admission, the second six months later. It may be assumed that concomitant and commensurate changes have taken place in the myocardium over this same period of time. We have the radiographic evidence of the return of the heart size to normal and the excellent clinical status of our patient to support this contention.

Conclusion

A patient with hemochromatosis who exhibited heart failure has been presented. He continues to do well, free of symptoms of cardiac failure, to the present time (a period of three years). A total of 31.25 gm. (62,500 ml.) of blood was removed by means of 125 venesections over this period of time. The patient expends at least four to five hours of vigorous effort as a farmer without untoward effects.

It is planned to continue the program of repeated phlebotomy, thus insuring that his hemoglobin concentration remains at slightly anemic levels. By so doing, it is hoped to prevent the re-accumulation of hemosiderin in his tissues.[20, 21, 23]

Certain theoretic considerations are offered as explanations for the objective and subjective improvement experienced by our patient.

Addendum

The patient was admitted for re-evaluation on January 4, 1960, and discharged January 22, 1960. He stated that he has recently felt better than at any time in his life. On examination the heart was not enlarged. The blood pressure was 130/80 mm. Hg; pulse, 80, with a regular rhythm. The liver was felt 1 cm. below the right costal margin. Hemoglobin, 11.7 gm.%; bromsulfalein, 1% retention. Chest x-ray was within normal limits. The electrocardiogram showed no change from the last tracing. Liver biopsy (Figure 5) showed almost complete absence of hemosiderin in the iron stain. Hematoxylin and eosin stain of liver specimen showed a decrease in the degree of cirrhosis (Figure 6).

A total of 130 phlebotomies has been performed, with removal of approximately 33 gm. of iron.

FIG. 5. Iron stain × 40, showing almost complete absence of hemosiderin (1/4/60).

FIG. 6. Hematoxylin and eosin stain × 40, showing considerable decrease in cirrhotic process (1/4/60).

SUMMARIO IN INTERLINGUA

Le advento de insulina ha rendite possibile que patientes con hemochromatosis e diabete supervive un periodo de tempore sufficientemente longe pro que disfallimento cardiac pote disveloppar se. Illo es hodie un del causas principal de morte in iste morbo. Le prognose pro le patiente con hemochromatosis in qui insufficientia cardiac

ha supervenite ha usualmente essite que su curso clinic sequerea un rapide deterioration.

Es reportate le caso de un fermero de 45 annos de etate qui habeva hemochromatosis e in qui disfallimento cardiac se disveloppava quatro annos post le declaration de su diabete. Le disfallimento, de accordo con le norma classic, esseva dextero-lateral. In le roentgenogramma le corde presentava un apparentia diffusemente allargate. Le electrocardiogramma exhibiva nonspecific alterationes de STT. Sub le conditiones de un programma de venesectiones septimanal—con le prisa usual de 500 cm^3 de sanguine—mantenite durante un periodo de tres annos, le disfallimento cardiac non ha recurrite in despecto de quatro a cinque horas de pesante activitate diurne como fermero. Assi un total de 31,25 g de ferro ha essite removite. Repetite radiographias thoracic ha monstrate que le contorno del corde ha retornate al norma. Le repetition del biopsia hepatic ha monstrate un marcate reduction in le quantitate de hemosiderina presente. Tamen, electrocardiogrammas in serie revela nulle alteration del configurationes depost le prime studio. Es discutite le stato currente de nostre cognoscentias relative al pathogenese de hemochromatosis.

A parte omne consideration theoric, repetite venesectiones—effectuate con consequentia usque al puncto de un moderate anemia e postea attenuate verso le mantenentia de un tal anemia—offere al patiente con hemochromatosis e disfallimento cardiac un bon prospecto de superviventia prolongate.

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KEROSENE PNEUMONITIS TREATED WITH ADRENAL STEROIDS *

By Robert L. Mayock, M.D., F.A.C.P., Nourallah Bozorgnia, M.D.,† and Harry F. Zinsser, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

Crude oil and the various fractions derived from it, such as gasoline and kerosene, have toxic properties on inhalation and ingestion that involve principally the central nervous system, liver, kidneys, lungs, and heart.[1]

Many cases of kerosene poisoning—and frequent deaths—have been reported as a result of accidental ingestion. Bain [2] reported that 25% of accidental poisoning deaths in the United States in 1949 and 1950 were due to kerosene; however, this syndrome occurs usually in children in rural areas [3] where kerosene is more in use.

The subject of this report is an adult male who developed a pneumonitis with liver damage after the accidental ingestion of Ultrasene,† a kerosene product. His disease ran a protracted course that remitted after steroid therapy on two different occasions. Our observations, combined with those made previously on a case reported by Graham,[4] suggest that steroids are therapeutically effective in this condition.

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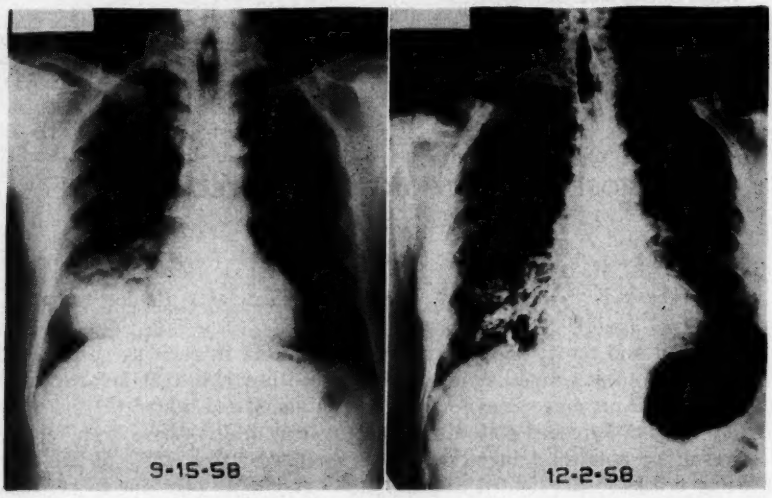
† According to Dr. Robert J. Bower, Medical Director of The Atlantic Refining Company, the composition of Ultrasene is as follows: "Ultrasene is a heavily acid treated, narrow boiling range, kerosene material. Boiling range of 400 to 500° F. It has an average composition of: 70% paraffins, 28% naphthenes, 2% aromatics, .01 to .02% sulfur; specific gravity, 0.783; 60° F."

Case Report

A 55-year-old Negro male was admitted to the Hospital of the University of Pennsylvania on August 31, 1958, because of cough, fever, shortness of breath, and pleuritic pain. He had been in good health until 1:30 p.m. on August 29, 1958, two days prior to admission. While working at an oil refinery he had accidentally drunk several mouthfuls of Ultrasene, under the impression that he was drinking water. At least one mouthful was swallowed, and choking with severe coughing ensued, some of the liquid coming out of his nose. At the refinery dispensary he was given some milk of magnesia and was advised to drink plenty of water and liquids. Six hours after ingesting the kerosene, nausea developed and he vomited once. The vomitus consisted of food and bile; no gross blood was noted. He felt feverish and



A B

Fig. 1. (A). Chest roentgenogram (left) taken on 9/15/58, shows pneumonia predominantly in the right middle lobe. (B). Subsequent bronchogram (right), taken on 12/2/58, reveals that bronchiectasis was confined to the right middle lobe area.

short of breath, and had an occasional dry cough, but no chest pain or chills. The next day the cough was more frequent, and was productive of about one-half cup per day of grossly bloody sputum. The patient developed pleuritic pain in the right side of the chest, and was sent to the hospital on August 31, 1958.

Physical examination on admission revealed a temperature of 103° F.; pulse, 120 per minute; respiratory rate, 24 per minute; blood pressure, 130/74 mm. Hg. The patient was in moderate respiratory distress; he was orthopneic but not cyanotic. The pupils were small and responded poorly to light. His ocular fundi showed grade 1 arteriosclerotic changes. The nasal mucosa was slightly congested, with exudate present, and the throat was slightly injected.

Physical examination of the lungs revealed decreased breath sounds over the right base and the right middle lobe, with wheezes, rhonchi, and moist râles over the same area. Examination of the heart was negative except for the presence of a sinus tachycardia. The remainder of the physical examination was negative.

On examination the sputum was grossly bloody, tenacious, and mucoid. Bac-

teriologic examination of the sputum showed micrococci, alpha streptococci, neisseria, and diphtheroids.

Laboratory studies showed a hemoglobin of 15.8 gm.% and a white cell count of 13,900 per cubic millimeter, with 81% polymorphonuclear leukocytes, 4% monocytes, and 15% lymphocytes. By the time of discharge the white count had gradually come down to 3,900 per cubic millimeter. On admission, urinalysis showed 1- to 2-plus protein, with very rare red cells, occasional white cells, and occasional epithelial cells. By the time of discharge the urine was normal.

The fasting blood sugar was 94 mg.%; the blood urea nitrogen was 11 mg.%, and it remained normal throughout the patient's stay. A phenolsulfonphthalein test showed 35% excretion in 15 minutes and 72% in 120 minutes. Total serum proteins

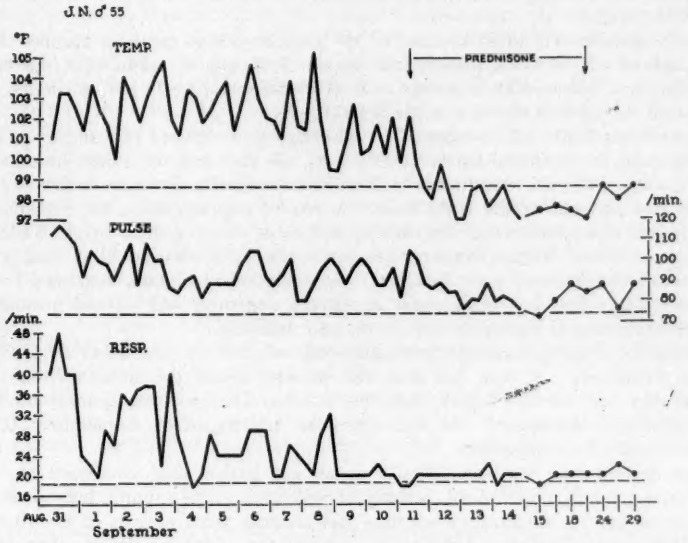


FIG. 2. Response of patient's fever subsequent to the administration of prednisone. The patient's symptoms, physical findings and x-rays also improved subsequent to the use of prednisone. Twenty days after prednisone was stopped a relapse occurred, with improvement when steroids were administered again.

were 6.1 gm.%, with an albumin of 3.7 gm.% and a globulin of 2.4 gm.%. Liver function studies were as follows: direct bilirubin, 0.14 mg.%; total bilirubin, 0.80 mg.%; cephalin flocculation, 0; thymol turbidity, 1.4 units; zinc turbidity, 4.2 units. A bromsulfalein test on September 6 showed a 41.7% retention in 45 minutes, but this had regressed to 9.1% by September 16, 1958. Serum pyruvic transaminase was 30 units (Karmen method) on September 6, 1958, and rose to 69 units by September 15, 1958. The alkaline phosphatase was 6.9 units (Jones-Reinhardt) on September 6, 1958, 8.4 units on September 9, 99.6 units on September 15, and 9.1 units on September 16, 1958. We were unable to explain the sudden rise and fall of alkaline phosphatase, but upon review it could not be accounted for by any obvious laboratory error.

The chest roentgenogram revealed extensive consolidation involving the right middle lobe and the right lower lobe (Figure 1). The lungs otherwise were clear. An electrocardiogram was normal.

On September 2, 1958, the patient was placed on penicillin, 600,000 units intramuscularly twice a day, with no apparent effect. Penicillin was continued throughout his hospital stay, and he received analgesics for the right pleuritic pain.

The patient maintained a fluctuating temperature (up to 105° F., with an average of from 101° to 103° F.) until September 9, 1958, when his temperature came down to a lower level (100° to 102° F.—Figure 2).

The patient continued to have a productive cough with tenacious, greenish yellow mucoid sputum in amounts of 60 to 90 ml. per day, with frequent episodes of hemoptysis (up to two teaspoonfuls a day). A repeat chest roentgenogram on September 9, 1958, showed an air and fluid level in the right midlung field, with the left lung and right upper lobe remaining clear. Bronchoscopy was considered to institute drainage of the abscess, but this was postponed in the hope that it would clear with postural drainage.

On September 11, 1958, because of the case report of Graham recalled by one of the authors (H. Z.), the patient was placed on 15 mg. of prednisone four times a day. This was followed by a prompt lysis of his temperature to normal limits, where it remained throughout the rest of his hospital stay.

The patient improved considerably. Although he continued to bring up yellowish green sputum, the amounts decreased to 30 ml. per day and the cough became much less frequent. Physical examination of his chest revealed a decrease in the expiratory wheezes and rhonchi at the right base. A roentgenogram taken on September 15, 1958, showed disappearance of the abscess and some clearing of the right middle and right lower lobes. X-ray examination one week later showed slow and gradual clearance of the diseased area; however, a considerable residuum remained.

During this time the sputum was repeatedly examined and showed normal flora, with the exception of a candida species on two occasions.

The dose of prednisone was gradually reduced, and on September 20, 1958, was stopped completely. It was felt that the patient would not benefit from further hospital stay, and it was hoped that the residual changes and sputum production would gradually disappear. He was therefore discharged on September 30, 1958, to be followed as an outpatient.

The patient was seen periodically as an out patient and continued to have a cough productive of about 15 ml. per day of yellowish green sputum, but no shortness of breath or fever. Expiratory wheezes and rhonchi were present in his right base and middle lobe. He was placed on bronchodilators (equal parts of phenylephrine hydrochloride, 1:200, and isoproterenol hydrochloride, 1:200) by hand nebulizer, and was advised to continue postural drainage.

On October 10, 1958, the patient again developed a fever of 100° F., recurrent bouts of small hemoptysis, bringing up two to three teaspoonfuls of blood, slight exertional dyspnea, and a considerable increase in his cough and yellowish sputum. He was therefore started on steroids again, in the form of triamcinolone, 4 mg. three times a day, on October 10, 1958. The fever disappeared within two days, and his symptoms subsided, except for the productive cough and occasional hemoptysis.

A chest roentgenogram taken on October 14, 1958, showed further improvement in the pneumonic process of the right lower lung field, but considerable residual change remained in the right middle lobe. Because it was suspected that the patient had a residual bronchiectasis of the right middle lobe, further study was advised. He discontinued his triamcinolone about November 9, 1958, before rehospitalization.

Second Admission: On November 10, 1958, the patient was readmitted to the hospital. A bronchoscopy revealed no evidence of abnormality. There were no abnormal secretions, and bacteriologic studies failed to reveal any significant organisms. Cytology of bronchial secretions was reported as class 1 (normal).

A right-sided bronchogram showed bronchiectasis of the right middle lobe. The

remainder of the bronchi of the right lung appeared to be normal. It was felt that the patient would not benefit from further medical therapy, since his symptoms had not cleared up with continued steroid therapy, and he had a residual cough productive of yellowish sputum, with frequent hemoptysis. He was discharged on November 15, 1958, with the plan to readmit him at a later date for surgery.

Third Admission: On November 30, 1958, the patient was readmitted to the hospital, and on December 5, 1958, he was operated upon by the thoracic surgeon. The chest was entered through an incision in the fifth right intercostal space extending from the costochondral cartilage anteriorly back to within approximately 5 cm. of the paravertebral muscles posteriorly.

When the chest cavity was entered it was noted that there was no free fluid in the pleural cavity, and the entire lung looked quite normal, with the exception of some adhesions to the diaphragm and to the middle mediastinum. It was very difficult to identify the fissure between the right middle lobe and the right upper lobe; therefore, the removal of the right middle lobe was performed in a segmental fashion.

Pathologic Report: "Gross description: The specimen consists of the right middle lobe of the lung. It is 2 by 7.5 by 12 cm. in greatest diameter and weighs 80 gm. The pleura is smooth and no scars are seen. The central portion of the lung is moderately firm to palpation. The bronchi were traced by opening, and they appear dilated in areas of the lobe. No tumor or obstruction is seen.

"Microscopic: The lung parenchyma shows vascular congestion and hemorrhage in areas. The bronchi have extensive destruction and fibrous replacement in their walls. They appear dilated. The mucosa is intact in the bronchi and bronchioles. Portions of the lung tissue appear emphysematous. There are large sheets of large lipid-containing macrophages in areas. These stain positively for fat content. Other macrophages containing hemosiderin are numerous, and there are many eosinophils.

"Diagnosis: Lipoid pneumonia, secondary to ingestion of kerosene, right middle lobe. Bronchiectasis, moderate, right middle lobe."

The patient tolerated the procedure well and had an uneventful postoperative course. He was discharged on December 17, 1958, and has been seen periodically as an outpatient. He has been asymptomatic and well, without any residua.

Discussion

The disease processes produced in humans by petroleum and its fractions are related to the volatility of the compounds and to the mode of entry into the body. The fractions, arranged in order of volatility,[5] are gases, alcohols, gasoline, kerosene, heating oil, lubricating oil, wax, residual oil, and asphalt. All of these fractions are a complex mixture of compounds. The fractions most commonly available for accidental ingestion are gasoline, kerosene, and lubricating oil (mineral oil). The most volatile fraction, gasoline, can produce death on inhalation of the vapor,[6] and on ingestion it is rapidly absorbed, with damage to the central nervous system, liver, kidneys, lungs, and heart. On the other hand, mineral oil is harmless by mouth but acts locally on the tissues to produce damage, such as oil pneumonitis[7] in the lungs and paraffinoma in the subcutaneous tissues. Kerosene, being midway between these two compounds in volatility, shares the toxic properties of both. As a result of the clinical observations and experimental studies in animals of Waring[8] and others,[9-12] the action of kerosene in producing disease has in part been explained. Waring demonstrated that if kerosene was introduced into the stomach of dogs with none entering the tracheobronchial tree, systemic disease without respiratory changes was usually found. Even with 100 ml. doses, relatively mild symptoms

were seen. However, after intratracheal instillation of as little as 7 ml. of kerosene, dogs developed convulsive twitchings, cyanosis, dyspnea, and pulmonary edema, followed by death. This sequence of events could be due to the intense changes involving the lung, with inflammation, edema, and bronchospasm. However, systemic absorption is greater apparently from the pulmonary route, as demonstrated by the findings of liver, kidney, heart, and central nervous system damage.[1]

In children the clinical picture is similarly variable.[1, 13-16] Large quantities of kerosene have been consumed with no apparent toxic reactions. In those cases where the kerosene was aspirated either while drinking or with subsequent vomiting, a much more dramatic picture is seen, with coma, convulsions, cyanosis, rapid shallow respirations, shock, and pulmonary edema. Fatalities usually occurred between two and 18 hours after ingestion. If the patients survived, evidences of pneumonia and damage to the visceral organs appeared, which usually cleared by the seventh to the tenth day. In cases of kerosene ingestion, attempts are directed toward avoiding vomiting, with resultant aspiration and damage.

The adult case of Graham [4] involved a workman who aspirated crude oil after falling into a tank. He had extensive pulmonary changes which ran a chronic course, after the acute symptoms with coma had subsided. This patient was treated with cortisone and ACTH, with subsidence of his symptoms. Each time his medications were stopped or reduced over the 11-month period, fever and symptoms returned.

The evidence indicates that adrenal steroids had an ameliorating effect in our patient, also. Both subjective and objective improvement occurred within 24 hours after starting therapy. There was a prompt decrease or disappearance of cough, pain, sputum, and malaise, with lysis of the fever and x-ray improvement. The relapse occurring 20 days later, which responded to steroids within 48 hours, adds further evidence in favor of this concept.

These two adults ran a prolonged course, the mechanism of which is not entirely clear. By contrast, children tend to run a more acute course. The possibility of benefit from the use of steroids in acute toxicity from kerosene has been raised by the report of Nassau.[17] He reported three children who had ingested kerosene one-half hour, three-quarters of an hour, and one hour, respectively, before being seen by him. They were in critical condition, but improved subsequent to the injection of 50 mg. of cortisone. Nassau felt that relief of bronchospasm could best explain the dramatic response that occurred. The significance of his observations is difficult to evaluate in light of the ordinarily rapid response of many children without steroids. Further evaluation of steroids in kerosene poisoning with animal experimentation would be worth while.

Summary and Conclusions

1. An adult patient developed a severe pneumonitis, with subsequent bronchiectasis and mild liver damage, secondary to the accidental ingestion and inhalation of a kerosene preparation (Ultrasene).

2. He improved dramatically following administration of steroids, relapsed upon their withdrawal, and responded when steroids were administered again.

3. Adrenal steroids may prove useful in the treatment of toxic pneumonitis secondary to inhalation or ingestion of kerosene or other related hydrocarbons.

Summario in Interlingua

Es reportate le caso de un patiente in qui un grado sever de pneumonitis sequeva le ingestion e inhalation accidental de "Ultrasene", que es un producto de kerosen. Intra sex horas post le accidente, ille disveloppava nausea. Ille vomiva un vice. Le subsequente symptomas includeva febre, dyspnea, tusse, dolores thoracic, e hemoptysis. Ille disveloppava signos physic e roentgenographic de pneumonitis in le lobos dextero-inferior e dextero-medie. Signos biochimic de injuria hepatic esseva etiam presente.

Quando nulle melioration clinic o radiographic habeva occurrite al fin de 11 dies, un curso de prednisona esseva initiate. Isto resultava in melioration del tusse e del production de sputo. Le febre se resolveva promptemente, e le constatationes roentgenographic se meliorava. Le therapia steroidic esseva continuate durante novem dies. Postea, illo esseva discontinuate gradualmente. Vinti dies post le cessation del therapia, le patiente experientiava un recidiva que esseva stabilisate promptemente per le re-application de prednisona. A causa del disveloppamento de bronchiectasis durante le periodo del pneumonitis, lobectomia dextero-medie esseva executate duo menses post le declaration del pneumonitis. Depost, le patiente se trova in bon stato de sanitate.

Le derivatos plus volatile de petroleo, per exemplo benzena, es plus toxic que le derivatos de plus basse volatilitate, como per exemplo le oleos de lubrication. Kerosen se rangia inter le duo extremos e ha reactiones toxic (per absorption systemic) si ben como irritation local. In animales, aspiration ad in le trachea plus tosto que absorption ab le vias gastro-intestinal pare esser le major base del toxicitate de kerosen.

Graham reportava un caso simile al nostre. In illo, le patiente suffreva un prolongate morbiditate con febre e symptomas pulmonar post le inhalation de oleo crude. Repetite remissiones esseva inducite per le uso de steroides e ACTH.

Super le base de nostre observationes e illos de Graham, nos conclude que steroides adrenal es utile in le tractamento de pneumonitis toxic que es causate per kerosen o altere simile hydrocarburos.

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SUDDEN DEATH IN ACUTE MYOCARDIAL INFARCTION: REPORT OF A CASE, WITH OBSERVATIONS ON THE CAUSE, PREVENTION, AND MANAGEMENT *

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SUDDEN death following acute myocardial infarction is a well recognized possibility. This unwelcome event, though more common in the first two weeks, may occur at any time after the onset of the myocardial infarction, and often occurs without warning at a time when clinically the patient seems stabilized. Sudden death has been reported to occur in 11.8% of patients with coronary sclerosis without occlusion, and in as high as 33.3% of patients with coronary occlusion.[1] This paper will report a case of sudden death after acute myocardial infarction, treated by cardiac massage, and will review the literature relating to this entity and its cause, prevention, and management.

CASE REPORT

A 45-year-old dentist was admitted to the Jackson Memorial Hospital at about 10:00 a.m. on June 6, 1959, with weakness and severe, squeezing, substernal pain, radiating down the left arm to the hand, of one and one-half hour's duration. A review of his family history revealed coronary heart disease and diabetes mellitus. The patient had no past history of heart disease. Except for the profuse sweating, pallor, and severe apprehension, the physical examination showed no abnormalities. An electrocardiogram taken within a few minutes of admission showed a normal sinus rhythm and the classic changes of acute posterior wall myocardial injury (Figure 1). As the pain was not relieved by 100 mg. of demerol and 1 gr. of papaverine intramuscularly, at about 10:30 a.m. the patient was given a left stellate

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ganglion block with 5 ml. of 1% procaine injected anteriorly via a paratracheal approach. This produced a Horner's sign and prompt relief of his chest pain. He also received 2 gr. of sodium phenobarbital intramuscularly, with some relief of his anxiety.

At about 10:50 a.m. the patient suddenly cried out and rapidly became unresponsive. His respirations ceased, no pulse could be felt, and no heart sounds were audible. Forceful precordial percussion and artificial respiration, begun immediately,

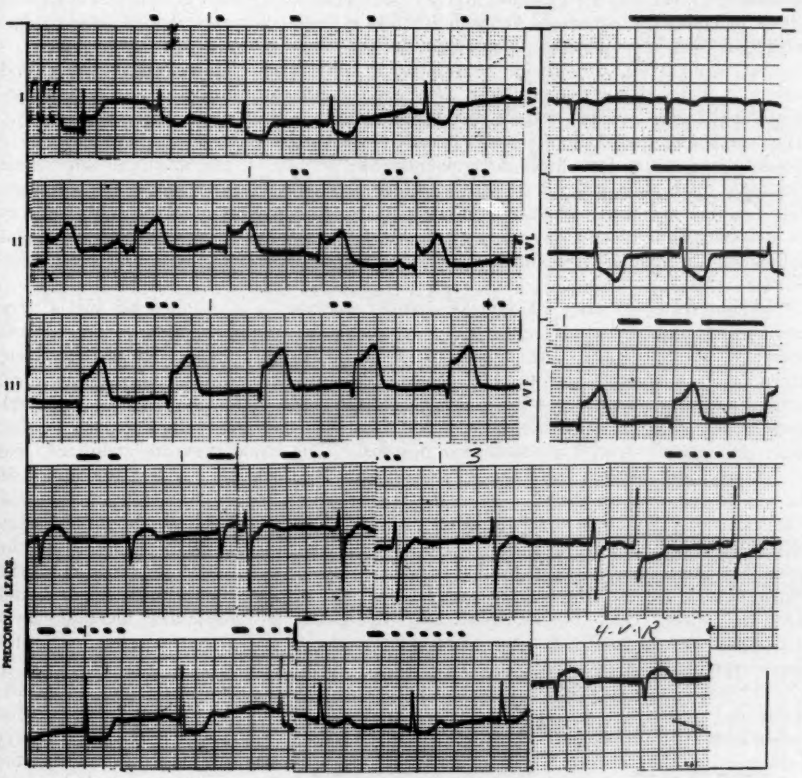

FIG. 1. Electrocardiogram prior to cardiac arrest, showing classic changes of acute posterior wall myocardial injury/infarction.

were without response. A surgeon present obtained a scalpel and, with a delay of not more than three minutes from the outcry, incised the left fifth intercostal space from the sternum to the anterior axillary line. The ribs were spread manually, a hand was inserted, and cardiac massage was begun through the intact pericardium. No bleeding was encountered at the incision, and the heart was motionless to inspection and palpation. Artificial respiration was continued by alternate pressure on the intact right chest until an anesthesia machine, mask, endotracheal tube, and oxygen were assembled. The cyanosis rapidly cleared on manual systole, and within 12 minutes the patient babbled incoherently and was breathing on his own. The incision was enlarged by severing the fourth costal cartilage, a self-retaining retractor

was placed, the pericardium was incised widely, and a plastic cannula was inserted in a left ankle vein. The duration of actual massage is difficult to determine precisely, but it was continued intermittently for at least two hours before a stable cardiac action was established. During this period the monitoring electrocardiogram showed the gamut of atrial and ventricular arrhythmias. Electric defibrillation was successfully carried out twice, 1 ml. of 1:1,000 epinephrine being injected each time into the left ventricular cavity under direct vision. Levarterenol (Levophed) was continuously administered via the leg cannula, and on one occasion 0.8 mg. of lanatoside C was given to combat a persistent atrial flutter; this resulted in ventricular tachycardia, which, in turn, responded to procaine amide (Pronestyl).

At about 1:00 p.m., under nitrous oxide anesthesia, the left chest was closed around a water-seal suction catheter, leaving the pericardium open, and a monitor-pacemaker * was attached externally and used continuously for the succeeding 10 days. The instrument was set to start an external electrical pacemaker after five seconds of asystole, and did so four times, at approximately 18, 30, 34, and 42 hours after chest closure. Each time, after a few minutes, the radial pulse exceeded the pacemaker rate and the machine was successfully stopped. The patient also received 100 mg. of hydrocortisone twice a day, slowly and intravenously, in the hope of reducing septal inflammatory reaction and aiding conduction through the A-V node and conduction bundle.

About six hours after massage the patient was alert and oriented but had a hazy memory of the period of massage. Forty-eight hours after massage he became mentally obtunded and, although more lucid at times, never regained complete clarity. A satisfactory urine output was not obtained until the fifth day. The blood urea nitrogen gradually rose to 76 mg.%, then dropped to normal after diuresis was established. The serum potassium reached 6.1 mEq., then gradually declined. Other than this, the electrolyte problem was minimal. The blood pressure stabilized, and the patient was weaned from the levarterenol on the fifth day. After the initial 48 hours the heart maintained a normal sinus rhythm, although a loud pericardial friction rub was audible until the fifteenth day. Frequent electrocardiograms, other than showing the previously mentioned arrhythmias during massage, indicated the usual evolution of a posterior wall myocardial infarction (Figure 2). On about the eleventh day, despite a good renal output, the patient began to accumulate presacral and leg edema, and became noticeably dyspneic. Intramuscular mercaptomerin (Thiomerin) was ineffective, but after cautious digitalization, intravenous mercaptomerin produced an excellent diuresis.

Physical and roentgen signs of right middle lobe pneumonitis and atelectasis came and went twice during the course, and tenacious mucus and persistent hiccups were recurring problems. The thoracotomy tube was removed on the fourth day; however, on the seventh day a quantity of fecal-smelling drainage came from the wound, necessitating replacement of the drain. A culture of the wound drainage revealed *Staphylococcus aureus,* coagulase-positive, and hemolytic streptococcus. Both of these organisms were only moderately sensitive to antibiotics. On the day of admission the patient had been started on penicillin, 4,800,000 units, and streptomycin, 2 gm. daily; and from the seventh day, antibiotics were given according to the results of frequent wound cultures and sensitivity studies. Systemically, chloramphenicol, novobiocin, and Colymycin were used; and topically, bacitracin, neomycin, and polymyxin. In addition, the patient received such nonspecific measures as fresh whole blood, tetanus toxoid, immune globulin, androgens, and, terminally, hypothermia. Despite these measures he continued to show a progressively rising fever, ranging as high as 104° F. On the sixteenth day the wound was re-explored and left open, with a vaseline gauze dressing and a catheter with water-seal suction.

* Manufactured by the Electrodyne Co., Inc., of Norwood, Massachusetts.

On the same day all antibiotics were stopped, and after several hours a blood culture was drawn. (This later proved to be sterile.) All antibiotics were withheld for 54 hours, and at first the patient's temperature abruptly fell, then rose to the former levels, with further deterioration of his general status. Intramuscular neo-

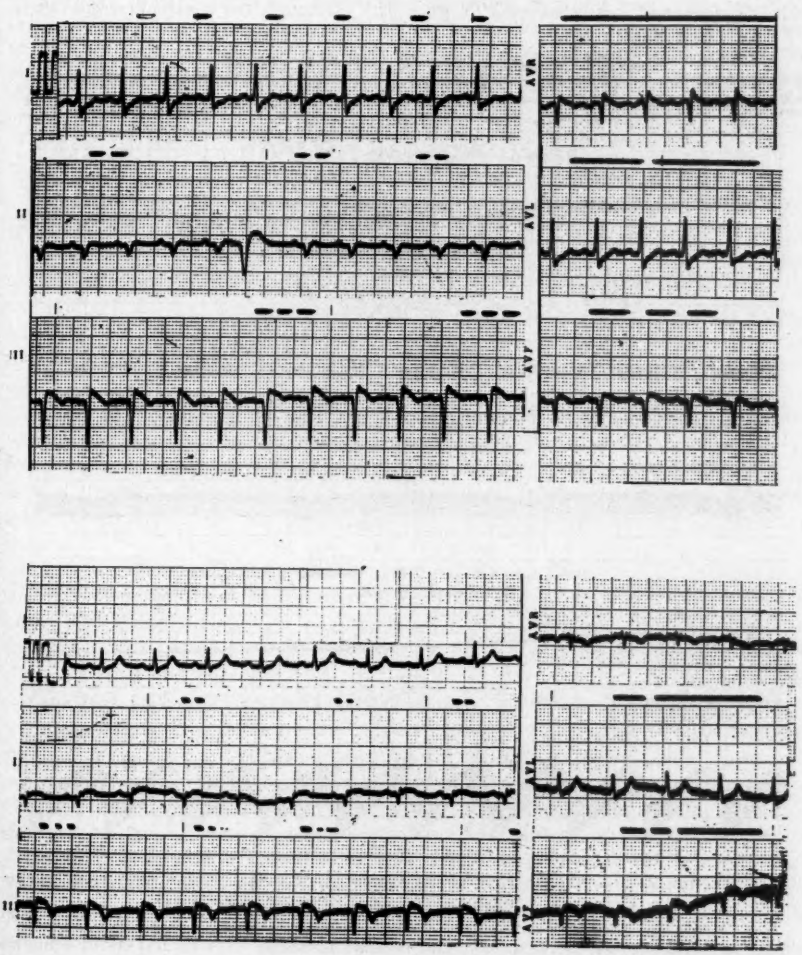

FIG. 2. Electrocardiogram on sixth (above) and sixteenth (below) hospital days, showing evolution of a recent transmural posterior wall myocardial infarction.

mycin was begun, and to this was added, in his final hours, Colymycin and a water-soluble nitrofuran. Wound cultures near the end of the course showed a coagulase-positive *Staph. aureus,* an alpha *Streptococcus viridans, Pseudomonas aeruginosa,* and *Proteus vulgaris,* each of which demonstrated a very limited antibiotic sensitivity. During the final 24 hours the blood pressure became difficult to support, even with

levarterenol, the renal output decreased markedly, and the patient's temperature rose rapidly. To control the fever he was wrapped in a thermal blanket and hypothermia was begun. In about 16 hours his temperature began to drop, reaching a low of 89.5° F., his blood pressure became unobtainable, and respirations had to be supported by mechanical means. Despite rewarming, the cardiac rate slowed, developed a slow nodal rhythm, and finally stopped (Figure 3). Although the pacemaker was begun

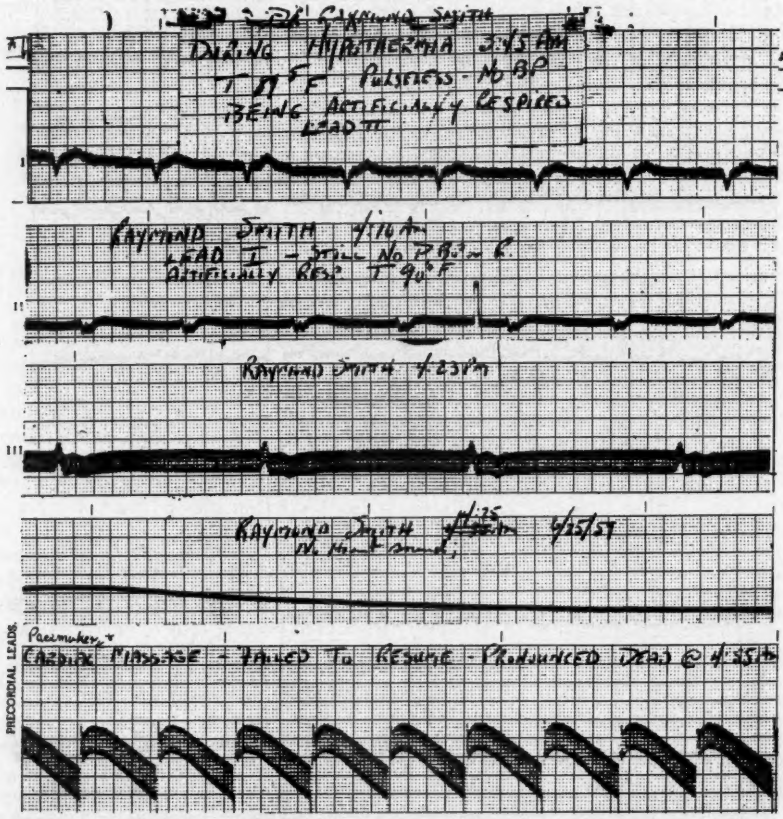

FIG. 3. Terminal electrocardiogram (Lead II only), showing an idioventricular rhythm ending in standstill, then the pacemaker deflections.

immediately, there was no response, and cardiac massage with injections of epinephrine was quickly instituted. Still the ventricular muscle gave not the slightest return of tone or contraction, and after some 30 minutes of this the patient was pronounced dead at the beginning of his twentieth hospital day.

Necropsy Findings: The thoracotomy wound edges were granular and, on section, showed epithelial hyperplasia with numerous microscopic abscesses. The heart, weighing 680 gm., showed a fibrinous pericarditis and bilateral ventricular hypertrophy. The right coronary artery was occluded 5 cm. from its ostium by a soft, gray thrombus superimposed upon an atherosclerotic plaque containing histologic evidence

of a recent hemorrhage into it. Proximal to this point, a fresh red thrombus had propagated 4 cm. toward the coronary ostium. Distal to the occlusion, and in the left and circumflex coronary arteries, were focal areas of atherosclerosis narrowing the lumen. The myocardium showed gross and microscopic evidence of a recent posterolateral-septal infarction. The area of the A-V node was not visualized histologically. In addition, miliary gross and microscopic abscesses were scattered throughout the myocardium, endocardium, and pericardium. The lungs showed gross and microscopic evidence of pleuritis, atelectasis, passive congestion, bronchopneumonia, and miliary abscesses and thrombosis of the artery to the left lower lobe. The spleen showed one infarct, and the kidneys and brain showed gross and microscopic abscesses.

Discussion

This 45-year-old, previously healthy man suffered a thrombosis of the right coronary artery with an extensive posterolateral-septal myocardial infarction and, two and one-half hours later, sudden circulatory arrest. Prompt cardiac massage effectively restored cardiac action; however, intractable infection led to his death 20 days later. The mechanism of his sudden cardiac arrest cannot be stated unequivocally. The heart, viewed and palpated through the pericardium, seemed to be motionless; however, it is easy to mistake a fine ventricular fibrillation for cardiac standstill under such circumstances. The precipitating factors of his cardiac arrest are equally difficult to state with certainty. The man was quite apprehensive and anxiety is frequently mentioned as a precipitating factor in cardiac arrest when there is also disease of the myocardium or conduction tissue. This may result from increased epinephrine output, producing ventricular fibrillation, or psychosomatic stimulation of the vagus-producing standstill.[2, 3] Cardiac arrest has been reported after stellate ganglion block,[4] and has been ascribed to rapid absorption of the procaine and/or idiosyncrasy to it. The patient was not known to be sensitive to procaine. Clinically, the arrest was thought to be due to inflammation and edema of the septum, including the A-V node and conduction bundles, as a result of the infarction. His clinical course and necropsy findings seem to support this impression. On this premise we started the hydrocortisone, hoping to reduce the inflammatory reaction and thus to aid conduction.[5] The cardiac massage and defibrillation did restore a satisfactory cardiac function despite his extensive infarction. At necropsy the only heart damage attributable to the trauma of massage was a fibrinous pericarditis. Therefore, from the cardiovascular standpoint, the massage was successful, though the overwhelming infection led to the patient's death. Such an overwhelming infection is very uncommon in this procedure.[2] The hydrocortisone which was continued because of his precarious general status may have hindered the body's defense mechanisms; however, whether this occurs is not clear from two carefully controlled studies.[6, 7] The use of hypothermia has been reported to be of value in overwhelming infections,[8, 9] and not harmful in experimental myocardial infarction.[10] It was therefore tried in a desperate attempt to control his rapidly rising temperature. Although his temperature dropped lower than we had planned, it never reached the usually accepted dangerous range. Cardiac massage during this second standstill produced not the slightest tone in the myocardium or suggestion of a spontaneous beat, and therefore was not prolonged.

The Problem of Sudden Death in Acute Myocardial Infarction

While sudden death in acute myocardial infarction may result from rupture of the myocardium or a massive pulmonary or systemic embolus, more commonly necropsy fails to show adequate cause for this event. In one series of 133 necropsies [11] on cases of recent myocardial infarction, 23% of the patients had had repeated precordial pain, but necropsy failed to show evidence of a recent extension of the infarct or other reason to account for the sudden death. Of this entire group, 77% had died suddenly and unexpectedly. In another series of 37 necropsies,[12] adequate pathologic explanation of the sudden demise was found in only three, each of whom had had myocardial rupture. This latter author presents terminal tracings on three of his patients, each of whom showed ventricular fibrillation and eventual standstill. It is stated that "a large percentage of patients dying suddenly of coronary artery occlusion do so following ventricular fibrillation." [2] However, Stroud and Feil [13a] reported terminal tracings on 23 of their own cases, and collected 164 terminal tracings from the literature. In the combined group there were 16 cases of "coronary heart disease" who died suddenly; of these, half showed ventricular fibrillation and half showed sudden ventricular standstill. Enselberg [13b] reported 16 cases of death following acute myocardial infarction, of whom 10 showed ventricular standstill terminally and six showed ventricular fibrillation. In 1958 Hellerstein and Turell [13c] reported a study of the mode of death in coronary artery disease in 73 patients. Of these patients 39.7% died suddenly and of the 13 cases in whom electrocardiograms were recording at the exact moment of death, 77% showed ventricular standstill and 23% ventricular fibrillation. The variance of the commonly accepted opinion from the facts reported may possibly be the result of transferring data from the experimental coronary ligation in dogs, which most commonly results in ventricular fibrillation.[14]

At the present time, in the standard texts of cardiology there is little or no mention of measures which might prevent this unfortunate event. The presently accepted therapy of acute myocardial infarction is bed rest, sedation, vasodilators and anticoagulants, and the appropriate treatment of any diagnosed arrhythmias. While these measures may be helpful—particularly the first two and the last—that they are not enough is evident to all internists. Therefore, we would like to discuss the possibility of preventive drug therapy to be applied routinely. At the present time there seems to be no measure that will prevent the sudden failure of myocardial contractility; however, ventricular fibrillation or standstill may possibly be preventable by drug therapy. The routine use of quinidine to prevent the onset of ventricular tachycardia and fibrillation first comes to mind, and this has been given a careful clinical trial in doses of up to 0.6 gm. every eight hours.[15] Not only was no protection afforded, but in the higher dosages the risk of sudden death seemed to be increased. Procaine amide (Pronestyl) has also been suggested for use "during the course of myocardial infarction as a prophylaxis against ventricular tachycardia and fibrillation once ventricular premature contractions are observed." [16] Ventricular tachycardia induced in dogs by the two-step coronary ligation technic is effectively suppressed by procaine amide,[17] and many internists have noted its salutary effect on ventricular premature systoles and ventricular tachycardia in humans. A search of the literature, however, fails to reveal a controlled study of the routine use

of procaine amide in acute myocardial infarction comparable to the one noted above on quinidine. Finally, our colleagues in anesthesiology and surgery seem to be firmly convinced of the value of atropine in the prevention of sudden death during surgery or delivery. They feel it blocks carotid sinus and vagovagal reflexes which are capable of depressing the sinus node and producing ventricular standstill. Although no one mentions these reflexes as the common initiating factor in the sudden death of acute myocardial infarction, atropine has been shown to reduce markedly the mortality after coronary ligation in dogs.[18] In addition, there is a report of atropine's being effective in inhibiting epinephrine-induced ventricular tachycardia in unanesthetized dogs.[19] In humans, there is a report of atropine's being effective in consistent inhibition of transient ventricular fibrillation in a case with established complete A-V dissociation.[20] Atropine was once advised for routine use in acute myocardial infarction for its supposed coronary vasodilating effect,[18, 21] but other studies failed to show any such effect.[22] A search of six currently used texts of cardiology shows that four [23-26] either make no mention of atropine in acute myocardial infarction, or clearly state that it has no use. The fifth recommends its use, without specific details,[27] and the sixth advises routine initial use to prevent vagovagal and carotid sinus reflexes and, in the event of pulmonary embolism, to prevent reflex vascular spasm.[28] Neither these nor a currently used text of pharmacology [29] mention any adverse effect of atropine in acute myocardial infarction. Although the commonly mentioned initiating factors in cardiac arrest and sudden death in acute myocardial infarction are (1) involvement of the nodal and conduction tissue, producing heart block and ventricular standstill; (2) ectopic ventricular rhythms arising in the borders of the ischemic areas, progressing to ventricular tachycardia and fibrillation;[30, 31] and (3) epinephrine released by anxiety, producing ventricular tachycardia and fibrillation, and although vagus innervation of the ventricles is a disputed point,[32] we feel that atropine deserves a carefully controlled study to evaluate its possible role in the prevention of this catastrophe.

When sudden death occurs in myocardial infarction, if the physician is present the customary therapy is forceful percussion of the precordium, artificial respiration, and needling of the heart blindly, with or without the injection of epinephrine. There are a few reports that one or more of these maneuvers were successful, but in the vast majority of instances they are fruitless. In 1954 Zoll [33] devised an external electrical pacemaker which has been recommended for routine use in myocardial infarction to treat sudden cardiac arrest.[34] Although this device has been most widely used in the treatment of Stokes-Adams attacks, it has been successfully used also in one reported case of arrest in acute myocardial infarction.[35] The instrument has since been combined with a device which monitors the cardiac electrical activity, and automatically sounds an audible alarm and actuates the preset external pacemaker when electrical activity of the heart ceases for a predetermined interval. Also integrated into the pacemaker is an oscilloscope that permits the operator to visualize the electrocardiogram continuously. This is the device mentioned in our case report. Its value for routine use in acute myocardial infarction might be questioned from three standpoints:

1. Good QRS complexes have been recorded in laboratory animals as long as five minutes after cessation of the visible heart beat;[2, 8, 36] thus the pacemaker

might not be started in time. Zoll [35] believes that this is not a valid objection for acute circulatory arrest, and that it occurs only in severely depressed hearts, in which case the circulatory failure would already have been evident for some time.

2. At least 50% of acute circulatory arrest in myocardial infarction results from the sudden onset of ventricular fibrillation, and this, too, would not actuate the pacemaker. The oscilloscope might show premonitory ventricular tachycardia; this, however, would require the constant attention of trained personnel, which might be possible with proper arrangements in an intensive treatment center.

3. Finally, in the event that sudden failure of myocardial contractility was the terminal mechanism, again the alarm and pacemaker would not be set off. Despite these limitations, it would seem that this machine should be utilized in a carefully controlled series of cases of acute myocardial infarction.

The therapeutic approach which, although heroic, seems to us to offer the most promising results at the present time, regardless of the mechanism of the circulatory arrest, is immediate thoracotomy and manual cardiac massage. The medical literature of the last six years records detailed reports on 13 cases where this was carried out. These cases are summarized in Table 1, along with another case received in personal communication from Reagan,[41] and our own case. In addition to these, we have brief reports of nine more cases. Thus, of the total of 24 cases known to us, 11 survived and 13 died. Unquestionably, there are many unreported cases and quite possibly most of them failed to survive, but we believe that, in a large number of such instances, if the details were known it would be found that, as in the report of McGregor,[42b] the delay in initiating massage exceeded five minutes. Only by accumulating detailed information on successfully and unsuccessfully treated cases will it be possible to evaluate this procedure in a statistically valid fashion.

The advent of chloroform anesthesia forced our surgical colleagues to face for the first time (in 1848 [2]) the problem of sudden and unexpected circulatory arrest. Several investigators, seeking the cause and an effective remedy, undertook studies in laboratory animals. As early as 1874 Moritz Schiff developed an effective technic of open thoracotomy and manual massage of the heart. This was first applied in the operating room with complete recovery by Kristian Igelsrud, of Tromso, Norway, in 1901, and first successfully applied on a hospital ward by Gray in 1905.[2] Today anesthesiologists and surgeons perform this procedure not infrequently, with remarkably good results if performed promptly. In contrast, internists have been slow to apply this technic to sudden death in acute myocardial infarction, although this was urged on internists in 1956.[38] The hesitance on the part of internists may be due to unfamiliarity with the technic, reluctance to perform any surgical procedure, particularly in the presence of acute myocardial infarction, infrequent opportunities, presumed need of special instruments available only in the operating room, concern over legal implications, unwarranted faith in the usual procedures, or simply the conviction that this technic is likely to be unsuccessful. We believe the time is at hand for the internist to overcome his previous prejudices, and to acquaint himself with the technic of cardiac massage and defibrillation so he will be prepared to carry it out in suitable instances. Obviously this procedure is not for the patient with terminal widespread malignancy, who is fortunate to have a myocardial infarction end his suffering, or for

TABLE 1

Cases of Cardiac Massage in Myocardial Infarction

Age Sex Date	Past Cor. Dis.	Site of Infarct	Time Until Massage	Heart Status	Length of Massage	Defibrillation	Drugs Used	Course	Final Outcome
55-yrs.; M; 4/13/53 Reagan[37]	None	High lat.	2 mins.	VF then VS	18 mins.	3×	Epinephrine	Uncomplicated; Dicumarol	Working as school custodian since disch.
46-yrs.; M; 3/11/55 Celio[38]	Chest pain, age 22	AWMI RBBB	3 mins.	VF	30 mins.	3×	None	Recurrent pain; heparin, antibiotics	Returned to work 4½ mos. after infarct as a carpenter
65-yrs.; M; 6/21/55 Beck[39]	None	Postero-lateral	5 mins.	VF	25 mins.	4×	Lanatoside C	Infected wound; antibiotics	Returned to med. practice in 1 yr.; alive & well
65-yrs.; M; 3/19/56 Hannon[40]	—	? AWMI	3½ mins.	VS	—	1×	Na lactate	Intractable wound infection; antibiotics	Died on 14th day of infection
33-yrs.; M; 5/2/56 Reagan[41]	—	Antero-lateral	2 mins.	VF	20 mins.	2×	None	Uneventful	Alive and well; driving milk truck
41-yrs.; M; 6/15/57 Bloomfield[42a]	None	AWMI	—	? VF	45 mins.	1×	Procaine amide Cal. chloride Aramine; antibiotics	Recurrent pain, empyema of 6 mos. duration	Alive & well; chronic anxiety reaction
50-yrs.; M; 0/00/00 Bloomfield[42a]	None	AWMI	—	VF	—	3×	None	Left hemiparesis	Returned to work in 3 mos. —real estate broker
39-yrs.; M; 1/31/57 McGregor[42b]	None	—	9 mins.	VS	2 hrs.	6×	Cal. chloride	Lived 1 hour	Necropsy: fresh occl., right circumflex A
53-yrs.; F; 2/2/57 McGregor[42b]	Yes	—	8 mins.	VF then VS	2 hrs.	Repeated	None	Maintained cardiac rhythm never established	Necropsy: old anteroseptal MI; fresh occl. of right coronary
51-yrs.; M; 7/18/57 McGregor[42b]	Yes	Antero-septal	1 min.	VF	30 mins.	2×	Procaine amide	Uncomplicated; anticoagulants	Mild exertional dyspnea and ang. pectoris 6 mos. Working ½ day as auto mechanic
71-yrs.; M; 0/00/00 McGregor[42b]	Yes	—	12 mins.	VF	2½ hrs.	Several times	Cal. chloride, epinephrine	Maintained cardiac rhythm never established	Necropsy: fresh occl. left ant. desc. 1 cm. from ostium
51-yrs.; M; 0/00/00 Conklin[42c]	None	AWMI	4½ mins.	VF	15 mins.	2×	Epinephrine, hydrocortisone, quinidine, antibiotics	Wound infection, pneumonitis; anticoagulants	Returned to work 7 mos. as chemist
53-yrs.; M; 8/24/58 Nickel[42d]	Yes	AWMI	3 mins.	VS	30 mins.	1×	Epinephrine, lanatoside C	Uneventful	Alive and well
40-yrs.; M; 9/19/58 Nickel[42d]	None	Antero-septal	3 mins.	VS	45 mins.	1×	Epinephrine	Uneventful	Alive and well
45-yrs.; M; 6/6/59 (authors)	None	PWMI	3 mins.	VS	2 hrs.	2×	Epinephrine, lanatoside C, Levophed, Pronestyl, Isuprel, antibiotics, hydrocortisone	Congest. failure, oliguria, intractable wound infection	Died of wound infection and septicemia 20th day

the 80-year-old invalid whose senility has long since taken him out of this world. Nor is it to be recommended in cases where more than five minutes have almost certainly elapsed since the cessation of the circulation. In any given case before the emergency arises we would urge the internist to give thought to the possible use of this technic, and to prepare for it if this course seems wise. For its successful application, four things are essential:

1. The internist must acquaint himself with the procedure.
2. The medical and nursing personnel of the hospital must be trained to back up the effort promptly.
3. Provision must be made for an emergency pack, such as is illustrated in Table 2, at the patient's bedside or a nearby nurses' station.
4. Provision must be made also for the rapid assembling of specialized personnel (anesthetist and thoracic surgeon) and equipment (anesthesia machine, oxygen, endotracheal tube, defibrillator). These obstacles are not insurmount-

TABLE 2*

To Open Chest:

1 scalpel
1 pair scissors (to cut cartilage and pericardium)
2 hemostats (to lift pericardium)
1 self-retaining retractor for ribs

To Ventilate Lungs:

Face mask
Rubber bag
Airway
Oxygen tank—100% oxygen

Medications:

Epinephrine, 1:1,000 (to increase myocardial tone)
Procaine, 1% (to reduce myocardial tone or irritability)
Lanatoside C
Isuprel for intravenous use
Levarterenol (Levophed)
Two c.c. syringes—2
Ten c.c. syringes—2
Needles, #26, two inches long—4

* Modified from Beck.[43]

able. There are two recent monographs [2, 3] dealing with cardiac resuscitation, and a number of excellent journal articles on the subject.[43-46] In addition to these sources of information, a two-day course in cardiac resuscitation is available through the Cleveland Heart Association. Although detailed information is available in the above cited references, we would like to discuss certain aspects of cardiac resuscitation and, where possible, apply it to acute myocardial infarction.

The initial problem is the prompt recognition of the circulatory arrest. Most commonly, this is a dramatic event in myocardial infarction, but, even so, valuable time may be lost by prolonged diagnostic procedures—there usually is not time to call a consultant or to send for an electrocardiograph. Unless oxygenated blood is got to the brain within four or at the very most five minutes, the chance of complete recovery becomes dramatically reduced.[36] The simplest criterion is the absence of a perceptible pulse or blood pressure. Auscultation of the pericordium would likely be carried out by the internist, and some authors

have advocated thrusting a long needle into the myocardium to note whether it moves. Still other, more time-consuming and less helpful maneuvers have been suggested. We would like to emphasize the great importance of making a prompt decision and not prolonging diagnostic procedures. In such an emergency situation, one might reasonably suppose that many errors would be made; however, in only six of 1,710 cases reported to the Cardiac Arrest Registry did thoracotomy reveal a beating heart.[2] It is true that, in some instances where this procedure is used after acute myocardial infarction, cardiac rupture or thrombo-embolic phenomena will have been the cause of death, but thoracotomy will not be a contributing factor.

Two instruments may prove of value in detecting acute cardiac arrest in myocardial infarction: the cardiac monitor-pacemaker, which has been discussed, and the electroencephalograph, which is even more sensitive. Perhaps the development of a small, inexpensive model of the latter instrument will make it available for this purpose.[2]

Once the diagnosis of circulatory arrest is made, a preplanned course of action must be carried out if resuscitation is to be accomplished. Percussion of the precordium is innocuous and not time-consuming if not prolonged. Blind needling of the heart and injection of epinephrine are not so innocuous—valuable time is often lost obtaining a needle, a coronary artery may be lacerated, and epinephrine may aggravate an existing ventricular fibrillation. If an external pacemaker is at the bedside, it may, with experience, be attached quickly and given a brief trial. Whatever is done, it is our contention that the precious four-minute limit must not be allowed to elapse before thoracotomy and massage are undertaken.

We will briefly outline the technic of cardiac massage and refer the reader to the articles previously cited.

1. Place the patient rapidly in a 10° Trendelenburg position.
2. Incise the left chest from the sternum to the midaxillary line through the the fourth or fifth intercostal space. (This has even been done successfully with a penknife.[47])
3. Slip the left hand between the ribs and behind the heart so that the apex lies in the palm, the fingers posteriorly, and the thumb over the left ventricle anteriorly.
4. Immediately begin forceful rhythmic massage at 60 to 80 times a minute, or at whatever rate is necessary to obtain a perceptible pulse.
5. Simultaneously with steps 1 and 2, have an assistant begin mouth-to-mouth respiration: occluding the patient's nose with one hand, he inhales deeply and exhales forcefully into the patient's mouth 20 times per minute.

With circulation re-established by manual systole, and ventilation of the lungs provided, the situation becomes much less pressing and can be controlled until auxiliary equipment and personnel can be assembled. Although mouth-to-mouth respiration can produce more than 90% arterial oxygen saturation,[48] it is best replaced by a mechanical respirator or anesthesia machine, delivering 100% oxygen, as soon as such equipment can be assembled. If ventricular fibrillation has been the mechanism of circulatory arrest, manual systole will revive the patient, but electric defibrillation will ultimately be necessary in the vast majority

of cases. There is at least one eventually successful case on record where two hours of massage elapsed before adequate defibrillation was accomplished. In ventricular standstill, a few squeezes will often suffice to start the heart again, though prolonged massage (up to eight hours [3]) may be necessary. If the myocardium does not "firm up" within five minutes, 0.3 to 1 ml. of 1:1,000 epinephrine injected into the chambers of the heart may be helpful. Many other drugs have their advocates, as will be found in the references. It is usually wise to place a cannula in an accessible vein to permit the administration of drugs such as levarterenol, lanatoside C, procaine amide and others, as indicated. When dependable cardiac action has persisted for from eight to 10 minutes, it is usually safe to close the chest; this is best delegated to a surgical colleague.

The subsequent care of the patient is that of the usual myocardial infarction, plus the care of the chest wound and any infection connected with it. Hypotension, arrhythmias, congestive failure, atelectasis, pneumonitis, and thromboembolic phenomena may be encountered, and are handled in the usual manner. Anticoagulants have been used without difficulty,[37, 38] and may indeed be particularly indicated after massage.[49] Serial electrocardiograms on four surviving cases from the surgical and obstetrical services of the Jackson Memorial Hospital showed nonspecific ST-T changes in two, and slight ST segment elevation suggestive of pericarditis in the other two. Thus one might expect the electrocardiograms to evolve in the usual manner, and to be little altered by the massage. The specific trauma to the heart produced by manual massage is surprisingly small. We reviewed the protocols and microscopic slides on five patients from the surgical and obstetrical services of the Jackson Memorial Hospital who died after survivals of varying duration. The findings varied from no perceptible abnormalities to fibrinous pericarditis, and microscopic hemorrhages or collections of inflammatory cells beneath the epicardium and within the myocardium. In these cases there were no gross abnormalities. A much more extensive study was carried out by Adelson [49] on 60 cases seen in a medical examiner's office. The only specific reference to myocardial infarction was the mention that the large, thin-walled capillaries adjacent to healed or healing infarcts seem particularly vulnerable to trauma. Adelson makes two other points of particular relevance to this paper: he noted no instance of traumatic thrombosis of a major coronary artery, and he noted fresh mural thrombi in the atria or ventricles of two patients who survived 12 hours or more. The care of the thoracotomy wound is best delegated to a surgical colleague. Infection of some degree is inevitable, but it is not often intractable. The role of prophylactic antibiotics is debated, but their use appears to be the common practice.

The prognosis of the patient with acute myocardial infarction who has been revived by cardiac massage cannot be stated at the present time because of inadequate reporting. However, 11 of the 24 cases known to us are long-term survivals, and are as able to continue in a gainful occupation as are other patients who have suffered a myocardial infarction. Of the 13 remaining cases, two survived more than two weeks, which raises the hope that, with more experience, the percentage of survivals can be improved. It must be remembered that the most important single factor in successful resuscitation is prompt (within four minutes) re-establishment of the flow of oxygenated blood to the brain. Statistics from the Cardiac Arrest Registry show an over all permanent survival rate

of 29% in 1,710 cases. Of these, 94% were massaged within the first four minutes. On the hospital ward, in 209 cases the over all survival rate dropped to 21.1%.[2] It is thought that the most important factor accounting for the difference is the delay in institution of massage. If this be so, the use of prearranged plans, such as that suggested by Seidman et al.,[50] would markedly improve these statistics. Underlying cardiac disease is frequently cited as a cause of failure of resuscitative efforts. However, in a study of 1,710 cases from the Cardiac Arrest Registry there was no evidence that younger and presumably less diseased hearts were more rapidly or permanently revived than were older hearts.[2]

Summary

Sudden death after acute myocardial infarction is not an infrequent event. Current modes of therapy seldom restore life. The authors feel that there are certain measures which deserve more thorough trial as preventive measures, and that the survival rate in this event would be much better if internists would resort promptly to thoracotomy and manual cardiac massage in selected cases. Salient points of causation, prevention, and detection of cardiac arrest and the technic of cardiac resuscitation and its prognosis are discussed, along with a review of the literature. Finally, an additional case is reported of sudden death from circulatory arrest after acute myocardial infarction which was treated by thoracotomy and manual systole.

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Summario in Interlingua

Le occurrentia de un morte subite es reportate in un tertio del casos de acute infarcimento myocardial. Le autores reporta un tal caso, tractate de urgentia per thoracotomia e massage cardiac manual con le resultato de un superviventia de 19 dies. Le morte resultava de septicemia irresistibile. Durante que in le passato il esseva opinate que in le majoritate del casos de iste genere le mechanismo del subite arresto circulatori esseva un fibrillation ventricular, on nunc recognosce que in plus que 70 pro cento del casos le mechanismo es un question de arresto ventricular. Le uso routinari de atropina durante le prime dies post le acute infarcimento myocardial—in le spero de prevenir un subite arresto ventricular—merita un meticulose investigation a controlo. Le application routinari del externe marca-passo de surveliantia in casos de acute infarcimento myocardial etiam merita un ben controlate proba. Le therapia traditional de iste adverse evenimento se ha provate relativemente inefficace, e le autores opina que in seligite casos, thoracotomia de urgentia—si necessari, per medio de un cultello de tasca—e le prompte systolation manual offere le melior promissa de superviventia. Le technica de iste modo de intervention es describite brevemente, e referentias a plus extense discussiones es appendite. Le expectate alterationes electrocardiographic e le subjacente alterationes anatomic que resulta intra le corde ab le systole manual es etiam discutite.

Un revista de 24 casos—publicate e non publicate—revela que in 11 le patiente superviveva. In omne iste 11 casos—con un exception—le patientes retornava al

travalio, usualmente in lor previe occupation. In le dece-prime caso, le patiente es invalidate per consequentia de un reaction de anxietate.

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EDITORIALS

PROPOSITI, PHYSICIANS, AND PAPERS

Elsewhere in this number of the ANNALS is a review of a book, weighty in mass and content, *The Metabolic Basis of Inherited Disease.*[1] The conceptual view this new work exemplifies was first set forth in 1909 by Garrod in his little book, *Inborn Errors of Metabolism.*[2] His work, with great implications for the future, received so little notice at the time that Garrison [3] gave several pages in his *History* to Galton and Pearson, then eminent in human genetics, but he did not even mention Garrod's name.

The present vigor of medical genetics owes most to the brilliant use of newer chemical methods, which provide reliable analyses for substances not measured finely enough by the older, cruder chemistry. But biochemists should not rush to canonize themselves on these good works alone. Their work, admirable beyond any doubt, would not have succeeded had not physicians already studied the relatives of patients and established clearly these diseases as *genetic* disorders.

The physician who reads of the complex and elegant biochemical studies which have made of Garrod's lonely pursuit a respectable and impressive discipline may conclude that surely he can add nothing now. If he is the typical physician, he works far from an academic center. His laboratory, if he has one, is equipped for blood cell counts, for simple urinalysis, and perhaps for the determination of blood sugar and urea nitrogen. He has no Warburg apparatus, no spectrophotometer, no ultracentrifuge. Had he these devices, he would have no time to use them; nor would he know how. Even if he knew how to carry off the chemical studies which might fatten our knowledge of medical genetics, he must work alone. He has at his side no platoon of technicians paid from a Federal grant in five figures.

The chemical study of inherited disorders demands long training in technics, costly and elaborate equipment, many-handed assistance. But medical genetics still needs the simpler studies which the physician is well able to pursue. He should be aware that the academic investigators are, for some disorders, putting the cart before the horse, the label of genetic disease before the facts of clinical data. Examples are easily found in *The Metabolic Basis of Inherited Disease.* Wyngaarden, writing on xanthinuria (with xanthine stone formation) must note that:

> "In no instance has more than one case of xanthine stone formation been recorded in a single family . . . no statement can be made regarding genetic factors

[1] Stanbury, J. B., Wyngaarden, J. B., Fredrickson, D. S.: The metabolic basis of inherited disease. The Blakiston Div., McGraw-Hill Book Co., Inc., 1960.
[2] Garrod, A. E.: Inborn errors of metabolism. Oxford University Press, London, 1909.
[3] Garrison, F. H.: An introduction to the history of medicine. W. B. Saunders Co., Philadelphia, 1914.

involved in xanthine stone formation in general. Indeed the adult cases described may not be dependent upon inherited metabolic factors. . . ."

Of orotic aciduria, Huguley concludes that:

"There is strong presumption that the enzyme deficiency was genetic in origin; but since no other members of the family are known to have been affected, there is no proof that it is genetic. . . ."

For some forms of . . .

"inherited porphyria the metabolic abnormality cannot be shown to be genetically controlled but may be acquired or may possibly represent a new mutation."

The editors of this new text cannot be justly criticized for including metabolic defects not yet clearly shown to be of genetic origin. Their decision, based ultimately on Garrod's views, may yet prove to be sound. But to these questions, the physician may be the one to give the answers.

He is the man best placed to discover that a disease has a familial, and probably genetic, pattern. Because of his friendship with his patient, examination of the immediate family and other relatives will be his privilege if he wants it. If he practices in a rural area, he is better placed for this task than are his colleagues in the city, for in the country families are more closely knit. But the setting alone is not enough to make of the physician a student of genetic disease. He must have the *itch* to study what he sees. More than a "physician, one who practices the art of physic or healing," he must be a true doctor, "one who teaches," but one who teaches himself. Textbooks and journals are not source enough for the true doctor. The printed word of medical knowledge is not a finished and fixed work like the Holy Writ; it is a text in flux and true doctors write the revisions. For them, the patient and his disorders are the sources. From the patient comes the picture of disease; and from the patient and his family comes the picture of inherited disease.

To suggest that practitioners have made and will make the greatest additions to medical knowledge would be to disregard the evidence from our history. But from time to time, able physicians have shown how to engage in fruitful research in simple and clinical settings. One such man is William Pickles, who, while practicing in Aysgarth, a quiet village in Wensleydale, Yorkshire, carefully observed his patients, using those most elementary of clinical devices, the history and the physical examination. From his data he was the first to recognize Bornholm disease, or epidemic pleurodynia, in Great Britain. With the same simple method, he deduced accurately the incubation period of infectious hepatitis some years before interest in this disease reached a peak during the second World War. His work on hepatitis was sound enough to catch the attention of his more sophisticated colleagues in London whence he was called to lecture in authority. Pickles, invited to Boston to give a Cutter Lecture, pointed out that:

"Country districts have certain advantages for the study of epidemiologic problems and the ability of the observer is of secondary importance to his opportunities, which indeed are great." [4]

"The opportunities which indeed are great" pass before the eyes of physicians every day but are rarely seized. They are taken only by the right man with the right eye. A second example is found in the genetic studies of familial hypophosphatemia with rickets pursued in rural North Carolina by Winters and his colleagues. Starting with a few patients with this disorder, these doctors went down the country lanes and with the relatively simple aids of serum phosphorus determinations and bone films traced this disorder through a group of large families. So carefully and thoroughly did they follow this trail that their description of the genetics of this disease [5] is already a classic account. True, they were academicians, but what they did could be done by any lone physician who seizes "his opportunities, which indeed are great."

Let us grant that the urge to research is not a simple desire; it may spring in part from the wish for a kind of immortality. The physician is a man with a strong ego, and if he is an honest man, he will admit to himself that he would like to see his name in a place more likely to stand against the erosion of time than a prescription blank. A medical journal is a better choice; though the journal may not be as durable as a tombstone, the name on the title page may be savored by the physician's very self. Lamentably, the physician seized with this urge to see his name in print is apt to use the stale device, the "survey." Dusting off in the hospital archives the records of 100 patients with gyroma, he arranges the data from this retrospection into 16 tables, reviews the literature, and ships the result to an editor. No matter that the author emulates the practice of a certain eminent clinic —his child finds no ready home. The paper probably tells us nothing new about gyroma, it tells us of no new ways to treat gyroma, and at best it suggests some odds that might be recalled for a bedside wager. And seeing this, the editor will not readily take the waif.

The editor, and his readers, want papers that will put new chapters, or new paragraphs, or even new sentences, into textbooks; their stomachs will not take stale cuds. The physician who wants to see his name in print need not grumble that he works alone and without the apparatus of biochemistry. Let him follow the track laid out above, that of Pickles and Winters; let him turn to his proper study, the patient. The goal of his pursuit will be set by his training, his temperament, his site. But if he is in practice, he is well placed to add to the picture of genetic disease. He knows his patients well, and can readily examine their families. With the simplest means, if

[4] Pickles, W. N.: Epidemiology in country practice. New Engl. J. Med. 239: 419–427, Sept. 16, 1948.

[5] Winters, R. W., Graham, J. B., Williams, T. F., McFalls, V. W., Burnett, C. H.: A genetic study of familial hypophosphatemia and vitamin-D resistant rickets, with a review of the literature. Medicine 37: 97–142, May, 1958.

he has the itch, he may tell us what diseases are inherited and comfortably leave the pursuit of their metabolic intricacies to his colleagues who staff the glittering laboratory.

E. J. H.

CYSTIC FIBROSIS

It is very appropriate that the clinical staff conference of the National Institutes of Health, which is published in this issue of the ANNALS, considers the problem of cystic fibrosis of the pancreas by contrasting the classical picture seen in a young child with the more unusual clinical history of an adult who shows definite findings in keeping with this disease picture. The observation of this disease in the adult has become a reality now that more children with the traditional picture are growing into the adult age group, presumably as the result of prolonging their lives with more effective therapy. In recent years, the discovery of the sweat electrolyte abnormality and its importance, and a heightened awareness of the disease have led to the diagnosis of milder forms of this disorder which might have been undiagnosed previously. It has also become possible to include in this diagnostic category an increasing number of patients who exhibit only parts of the clinical picture. For example, patients with chronic pulmonary involvement or pancreatic insufficiency alone have been found to show abnormal sweat electrolyte values. In groups of adults who have chronic pulmonary disease without pancreatic insufficiency, a number of investigators have found a few patients with abnormal sweat electrolytes and considered these cases to be adult instances of cystic fibrosis. It is factors such as these that will turn the attention of the internist to the various problems of this disease.

A major consideration in the diagnosis and pathogenesis of cystic fibrosis is the further delineation of the nature of the abnormality in sodium and chloride secretion in sweat. Thus far, physiologic studies of sweating in persons with this disease have not adequately described the factors that control or account for the sweat gland abnormality in patients with cystic fibrosis. Recent evidence has emerged to suggest that the function of the sweat glands in this disease is similar in many ways to that of normal glands, while on the other hand they show higher secretory rates under environmental thermal stimulation, earlier fatigue, and greater instability during prolonged maximal stimulation.[1, 2]

The considerable knowledge of the physiology of sweating must be integrated with already existing data on cystic fibrosis. Questions such as the influence of salt load, age, acclimatization, and degree and type of

[1] Sibinga, M. S., Barbero, G. J.: Observations on spontaneous sweating; elevated night sweating rates in cystic fibrosis. To be published.

[2] Sibinga, M. S., Barbero, G. J.: Studies in the physiology of sweating in cystic fibrosis. I. Experimental sweat gland fatigue. Pediatrics (in press).

stimulus, certainly will require further study before sweat analysis for electrolytes can be clearly interpreted, particularly with regard to the adult group. Any analysis of sweating in the potential heterozygous individuals as a criterion for cystic fibrosis will depend on further elaboration of these factors.

It is also quite important that this disease become familiar to the clinician and clinical investigator outside of the pediatric group, since the problems presented by this disease may be of considerable importance in the understanding of other diseases, such as asthma and bronchiectasis, which confront the medical internist. The whole area of external glandular secretion has lagged far behind the impressive advances which have been made in the field of endocrine secretion. And yet, there are many puzzling difficulties in our comprehension of functional and pathologic disturbances of the various exocrine gland areas of man. Cystic fibrosis will be a potent stimulus for the acquisition of broader knowledge concerning the nature of the exocrine secretory process. One cannot help but be impressed with the fact that there may be more than concurrent chance between a finding of high electrolyte concentration in sweat and the secretory abnormality of the tracheal bronchial glandular system. Already certain evidence has suggested that there is some relationship between the electrolyte content and the highly viscous nature of a secretion.[3, 4] Elucidation of this relationship may shed light on the basic mechanisms of the disease and on its treatment, since the obstructive character of the secretion is the cause of the high mortality.

Of central importance has been the question of whether such secretory abnormalities result from a qualitative defect in various chemical constituents or from an increased rate of secretory production which occurs under certain conditions. Finally, the controlling mechanisms of glandular secretion have not been examined. Whether the abnormality originates at the glandular site or results from a more proximal component as the neural or neurohumeral cholinergic intermediate is still a significant question which will require exploration. It carries considerable hope to a pediatrician that this disease will also be subjected to the scrutiny of the internal medical community, which has been so able in its investigations of many other disease processes. This may be one of the diseases where both the pediatric and internal medical clinicians and investigators may find a common area of learning and of hope for what had been considered only a few years ago to be a hopeless and poorly understood disease.

GIULIO J. BARBERO, M.D.*

[3] Kwart, H., Shashoua, V. E.: The structure and constitution of mucus. Trans. N. Y. Acad. Sci. **19**: 595, 1957.

[4] Chernick, W. S., Barbero, G. J.: Composition of tracheobronchial secretions in cytic fibrosis of the pancreas and bronchiectasis. Pediatrics **24**: 739, 1959.

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THANK YOU, DOCTOR ACTON

WITH the January, 1961, issue, there came to an end the last editorial service to be performed in Baltimore. For almost 23 years, with the exception of an interval for war service, Dr. Conrad Acton of Baltimore has carefully screened each sheet of page-proof of each issue of the ANNALS. To him this task was a challenge in the unending battle against error, to this task he brought professional acumen and a dedicated thoroughness. To the former editorial staff he must have been a bulwark; to the new editorial staff he has been a great help in a time of transition. To all the readers of the ANNALS he has been an unseen guardian. Dr. Acton, we thank you.

J. R. E.

BOOK REVIEWS

The Metabolic Basis of Inherited Disease. Edited by JOHN B. STANBURY, M.D., JAMES B. WYNGAARDEN, M.D., and DONALD S. FREDRICKSON, M.D. 1,477 pages; 23.6 × 17 cm. 1960. The Blakiston Division, McGraw-Hill Book Company, Inc., New York, Toronto, and London. Price, $30.00.

About 60 years ago, the inborn errors of metabolism were described in a little book of 155 pages with 248 citations. Today our Garrods use 1,424 pages of text and 5,098 references. These facts are the physical measure of a great progress in clinical medicine.

In this massive work 46 contributors, largely from the Boston-Bethesda axis, have set down practically all that can be said on those disorders which stem from inherited metabolic defects. Each chapter presents for a single disease (or ones closely related) a historic prologue, a clinical description, the biochemical background for the metabolic disorder, the disorder itself, the genetic pattern, and the treatment, if any.

The chapters run the full range of excellence, with a distribution skewed to the better end. Clearly, most of the contributors have written from thorough knowledge of their topics, knowledge gained by some in highly original studies of pathogenesis, by others from exhaustive surveys of affected families. Stanbury's account of familial goiter clearly comes from a man immersed in a study of the biochemistry of this disorder, and the same persuasive quality marks the chapter by Conn and Streeten on periodic paralysis.

Other valuable and comprehensive accounts include those of hyperbilirubinemia, phenylketonuria, the adrenogenital syndromes, gout, the porphyrias, the hemoglobinopathies, familial hypophosphatemia with vitamin D-resistant rickets, and many more. In a book of this scope, defects always can be found. The discussion of renal tubular acidosis draws for its clinical description and genetic speculation on less than half the number of cases at hand for analysis in the literature. Consanguineous marriages between parents of some patients with the infantile form of the syndrome have not been noted, nor have cases with genetic implications in the European literature. In the short section on dicumarol intoxication, the sensitivity to this drug shown by rabbits, found by Link and his colleagues to be transmitted as a mendelian recessive trait, should have been mentioned. This fact has not yet caught the attention of hematologists, but perhaps they disregard it to their loss. The discussion of pseudo-pseudohypoparathyroidism looks on this disease picture as an incomplete form of pseudo-hypoparathyroidism and omits the equally defensible view that it is an entirely different disorder, one of the types of dyschondroplasias.

The editors have had to limit arbitrarily the range of inherited disorders included. They chose to omit the heritable disorders of connective tissue and bone, reviewed thoroughly by McKusick in his recent monograph. Some disorders which should lie within the editors' boundaries are not here. Argininosuccinic aciduria, as important a disease as orotic aciduria, was left out, a discrimination due to tolerable but probably parochial bias.

Certainly the size—and hence the cost—of this book is in part due to another editorial decision. Each chapter includes an account of the normal biochemistry of the metabolic system in which the defect, if known, lies. Omission of these summaries would have shortened the text by about 10%, but the cost of the book would have been cut by less. Therefore the editors, wisely, did not make this cut; thanks to them, the reader need not scurry about seeking the background he might need in textbooks, yearbooks, and a score of journals.

Other economies might have come from the inclusion of fewer tables, diagrams, and photographs, and from the use of a shorter index. But the generous use of illustrations, tabular and graphic, and the exhaustive index are among the admirable qualities of this book, and these aids easily justify their cost.

Physicians may look to the book for advice on treatment. For some disorders, such as periodic paralysis and cystinuria, reasonably explicit instructions are laid out. Most of the chapters give only the principles on which therapy is designed. But for diabetes mellitus, for which treatment alone can be the subject of a monograph, the principles of therapy are barely implied.

Despite the arbitrary and self-imposed limitations under which the editors and contributors have written, this book is and will be, for many years, the definitive text on the inherited disorders of metabolism. It is not the book to which the medical student will turn for an introduction to these topics. He should prefer Harris's *Human Biochemical Genetics,* a far shorter and more elegantly written text. But the older students, who have more than a superficial interest in these disorders—internists, pediatricians, biochemists, and pathologists—should own this book. They will find, in 10 or 20 years, that biochemical studies of the inherited disorders will have gone far beyond those set forth here, but they will still turn to this book for a complete account of these diseases as they are now known.

EDWARD J. HUTH, M.D.

The Year Book of Medicine (*1959–1960 Year Book Series*). Edited by PAUL B. BEESON, M.D., CARL MUSCHENHEIM, M.D., WILLIAM B. CASTLE, M.D., TINSLEY R. HARRISON, M.D., FRANZ J. INGELFINGER, M.D., and PHILIP K. BONDY, M.D. 733 pages; 22 × 14 cm. 1959. Year Book Publishers, Inc., Chicago, Ill. Price, $8.00.

A review of *The Year Book of Medicine* should point out that this book is one of the more popular efforts to summarize the wealth of literature confronting a reader interested in internal medicine and general practice. This volume of the *Year Book* can be criticized on some minor points.

Comparatively speaking, hematology is covered excessively, to the point of detail. The cardiovascular and renal diseases, probably the most important fields discussed, receive relatively little space. The cardiovascular section over-emphasizes physiologic and clinical research and skimps the voluminous chemical research going on in the field. Editorial comments concerning gastroenterology are longer than necessary, but they present more valuable supplementary references than do other sections.

Regardless of these criticisms, the excellent editorial comments, the fine supplementary references scattered throughout the book, and the ability of the editors to summarize so consistently the main points of articles clearly make this work an excellent endeavor, serving its purpose extremely effectively. Reading *The Year Book of Medicine* remains an excellent means of critically covering a broader expanse of literature than one can possibly cover alone. In this sense, it makes a valuable contribution.

EUGENE HILDRETH, M.D.

Fundamentals of Chest Roentgenology. By BENJAMIN FELSON, M.D. 269 pages; 450 illustrations; 238 figures. 1960. W. B. Saunders Company, Philadelphia.

In his introduction to *Fundamentals of Chest Roentgenology,* Doctor Felson considers and labels two schools of roentgen diagnosis. Adherents of the "Aunt Minnie" school recognize familiar shadows and so reach their diagnoses in the way

one recognizes and calls an old acquaintance by name—i.e., "Well, look at her. It's Aunt Minnie all right!" In the "skyscraper" school, one builds upon "a broad deep base of fundamental concepts . . . rising, thereby, to greater heights." Felson is, of course, a proponent of the latter school, for he asks, reasonably enough, "What does the 'Aunt Minnie' radiologist do when he meets a stranger?" His book is a remarkably concise and readable exposition of the broad fundamental concepts upon which one can build in solving the varied and complex problems of chest roentgenology.

Beginning with a general discussion of the uses and technics of fluoroscopy and radiography, he discusses in succession the localization of intrathoracic lesions; the lobes; the segments; the hila, vessels, and lymph nodes; the pleura; the extrapleural space; and the diaphragm. A final chapter considers the significance of some special roentgen signs and should prove especially helpful. The book also includes a tabulation of the anatomic variants observed by the author in 18,000 normal chest roentgenograms, and far more useful to the general reader, an excellent bibliography.

This is in no sense an encyclopedic text of the roentgen findings in specific lesions of the chest. As the author says, "This book deals primarily with fundamentals and considers specific disease entities only insofar as they illustrate . . . the principles discussed." It is, however, an extremely informative presentation of the rational approach to the roentgen diagnosis of chest lesions. The text is lucid and witty, the illustrations profuse and of good quality. Every physician who is interested in diseases of the chest, regardless of his specialty and experience, will find much of value in this volume.

WILLIAM J. TUDDENHAM, M.D.

A System of Medical Hypnosis. By AINSLIE MEARES, M.D., D.P.M. 467 pages; 16 × 24 cm. 1960. W. B. Saunders Company, Philadelphia. Price, $10.00.

The author, an Australian psychiatrist with wide experience in hypnosis, successfully attempts in this book "to offer the student, the practitioner, and the psychiatrist-in-training a guide to medical hypnosis which is essentially practical but which at the same time clearly relates the clinical procedures to the underlying psychodynamic principles."

The scope of the book is evidenced by the titles of its five main sections: I. The Nature of Hypnosis; II. The Induction of Hypnosis; III. Suggestive Therapy; IV. Hypnoanalysis; V. Hypnosis in General Medicine. The author specifically states that the book is not a textbook, in that it does not objectively describe and evaluate all of the current theories and practices of hypnosis. Rather, he states, "It aims to be a description of medical hypnosis as practiced by the author." As such, it contains a wealth of practical information and description, including many approaches and viewpoints which even the experienced hypnotist will find useful. However, since the impression is at times conveyed that certain of the author's clinical opinions are fact, when in reality they are quite controversial, the book should be read with the words "hypnosis as practiced by the author" constantly in mind.

Although the sections on suggestive therapy and hypnoanalysis are intended specifically for the psychiatrist, the nonpsychiatrist will find them interesting and informative. Dr. Meares writes with such interest and clarity that the apparent simplicity of using hypnosis in psychic disorders may tempt the nonpsychiatrist to embark on psychotherapeutic adventures beyond his competence. The need to understand thoroughly the psychodynamics of all patients before using hypnosis is presented by implication throughout, in statements such as, "The student has already been warned of the difficulty and complications of hypnosis with latent homosexuals, and he is advised that cases should be treated only by an experienced hypnotherapist."

The book obviously cannot and does not help the student to recognize latent homosexuality, a skill requiring some psychiatric training and experience. The author apparently feels that such training is a prerequisite to the use of hypnosis, but this point deserves further emphasis.

Clinical practice being what it is, psychiatrists using hypnosis will find many areas of disagreement with Dr. Meares. Among the most frequent will probably be the laying on of the hands used often by Dr. Meares to enhance the process of hypnosis. The constant palpation of the patient's abdomen during the process of hypnosis, too, would not be embraced by most American psychiatrists. The "direct stare" is likewise little used here. The author's emphasis on the "atavistic theory" is perhaps natural, since it is his own, but it is rather one-sided.

The above criticism notwithstanding, Dr. Meares has succeeded admirably in presenting his own system of hypnosis. In spite of his disavowal of the book as a textbook, it is the best orientation to hypnosis for both psychiatrists and non-psychiatrists currently available, and will probably find a place as a textbook in many courses on the subject.

SYDNEY E. PULVER, M.D.

Atlas of Clinical Hematology. By KATSUJI KATO, M.D. 1960. Grune & Stratton, New York. 296 pages, with 92 color plates. Price, $25.00.

This *Atlas,* by one of the foremost Japanese hematologists, consists primarily of representative slides of various disease states that he has collected over a 25-year period.

The *Atlas* begins with a short introduction of the author's theory of hemocytogenesis. A brief description of each of the various diseases is then given. Following each description, the color plates showing the blood cells of that disease are printed on the right-hand side. On the opposite side of the page there is an outline drawing of the cells, with a legend for these cells.

The descriptions of the diseases are adequate for an atlas, and at the end of each chapter there is a short but good list of references.

The *Atlas* has one great disadvantage. The plates are hand-drawn by the author and therefore represent his view of how the cells look. The color of many of the cells, especially in the neutrophilic and eosinophilic cells, is poor and often misleading. The shapes of many of the blast cells in the plates depicting acute leukemia are most bizarre. On many plates, cells that are obviously metamyelocytes are called myelocytes.

The use of old terms such as "chlorosis" and "von Jaksch-Hayem anemia" does not seem proper in a new book. A good color plate showing blood-loss anemia would seem most appropriate.

Plates 17, 19, and 27 list many cells as reticulocytes but there is no evidence presented that these smears were stained with a supravital stain.

In the text the author states that congenital hemolytic jaundice is "characterized by excessive intravascular blood destruction resulting from the action of hemolysins present in the plasma." This is certainly not the view held by most hematologists today. The inclusion of the description of acquired hemolytic anemia under the heading of congenital hemolytic jaundice is most confusing.

Many of the outline drawings identify the cells by letter, but the legends at the side of the drawings do not give the type of cell that corresponds to the letters. The reader, therefore, has to go looking through the pages to find the type of cell the author is describing.

Many typographic mistakes are also present.

In general, the outline of the book is good, and it is printed on good quality paper, but this reviewer is not sure that another atlas composed of drawings is necessary at this time. The reviewer does not believe this atlas has as much to offer as do many other atlases now available for students, practitioners, or hematologists.

HAROLD A. WURZEL, M.D.

Eye Signs in General Disease. By F. HERBERT HAESSLER, M.D., Professor Emeritus of Ophthalmology, Marquette University School of Medicine. 118 pages. 1960. Charles C Thomas, Springfield, Ill. Price, $5.75.

This brief reference manual presents, in outline form, a list of signs encountered in the routine examination of the eyes which may be helpful leads to the general practitioner, internist, neurologist, or other examiner in evaluation of the patient with systemic disease. It includes an introductory chapter on the procedure used in physical examination of the eyes. The main body of the book lists the signs encountered in examination of the ocular functions, including motility, the anterior segment, and the fundus. Each sign is briefly described and its diagnostic and prognostic importance is discussed briefly. Occasional references are included for the benefit of readers wishing to find illustrated material or more complete descriptions. An index is helpful for quick access to the discussion of any given sign. No illustrations are included.

Dr. Haessler brings to the reader the benefits of his many years of clinical experience in ophthalmology. Although the book tends to be dogmatic because of its brevity, it will, nevertheless, serve as a valuable reference for the practicing physician and should serve to enhance his diagnostic acumen and to enrich the enjoyment of his art.

WILLIAM C. FRAYER, M.D.

Expeditions Francaises a l'Himalaya: Aspect Medical. By JEAN RIVOLIER, with the collaboration of P. BIGET, F. FLORENCE, A. LAPRAS, and J. OUDOT. 229 pages; 24 × 17.5 cm. 1959. Hermann, Paris. (In French.) Price, 3.000 Fr. (paperbound).

Since Rusticiano suggested, in 1298, that the difficulties Marco Polo experienced in the mountains of Tibet were related to noxious effects of high altitude, man has been interested in "altitude medicine." In the last century, stimulated by desires of mountaineers to climb the peaks of the world's highest mountains as well as by new fields of aviation and space travel, scientists have been studying problems related to high altitude. Physicians and physiologists who have accompanied expeditions into the high Himalayan mountains have reported their observations of the climbers at various altitudes.

Between 1950 and 1955 several expeditions to the Himalayan mountains were undertaken by French explorers. The medical features of these trips are recorded in a series of papers collectively presented in *Expeditions Francaises a l'Himalaya: Aspect Medical.* The opening portion of the monograph reviews features of altitude medicine. There is a detailed clinical description of mountain sickness and a discussion of factors related to acclimatization to altitude. In addition, disturbances commonly incurred by mountaineers are enumerated and analyzed: cold exposure and frost-bite; snowblindness and sunburn; accidents with attendant traumatic injuries; and sudden cardiovascular deficiencies associated with severe effort at high altitude.

The remaining essays deal with separate expeditions and record observations made on a variety of subjects. Numerous diets were tested in France, and the best combinations of rations were then evaluated during the ascents. Acclimatization to altitude was studied extensively, and methods for most effective and rapid achievement of this state were evolved. Measurements were made on the following parameters before the trip, at various stages in the course of ascent to mountain peaks, and after the climbers' return to Paris: pulse rate, breath-holding times, resting minute ventilation, alveolar oxygen and carbon dioxide levels, and in some, hemoglobin saturation as detected by an oximeter. The uses of supplementary oxygen by inhalation were investigated. It was concluded that an open circuit system was the most practical for reasons of weight and safety. Rates of administration of oxygen needed to maintain efficiency during activity states at varying altitudes were defined.

Medical planning of such expeditions is highly complex, and some insight into the logistics of the projects can be gotten from discussions of the problems anticipated and encountered. Initial and final periods of march were through the tropical and subtropical forests and plains of Nepal. Here the major medical hazards were malaria, dysentery, snake bites, infestations with land leeches and intestinal parasites, and traumatic injuries. (While traversing Nepal, some of the medical diseases indigenous to the area were observed and recorded. The very primitive state of medical care available was also commented upon.) During initial ascent, varying degrees of mountain sickness were encountered. Anorexia and malnutrition contributed to malaise and poor performance. After variable periods of time, acclimatization developed and further ascents were made. Then stresses related to exposure, cold, sunburn and snowblindness, and oxygen-lack became predominant.

Careful observations of the effects of altitude and acclimatization on a variety of respiratory and circulatory parameters are especially useful. The French studies, herein detailed, represent additional information on which rational concepts of acclimatization to altitude and oxygen utilization in these circumstances can be based. Two extensive bibliographic chapters, dealing with pathophysiology at altitude and the effects of cold and nutrition on performance, add to the value of the monograph.

JEROME E. COHN, M.D.

Involution of the Ductus Arteriosus: A Morphological and Experimental Study, with a Critical Review of the Literature. (From the Department of Medicine—University of Rome; Director: Professor Luigi Condorelli). By A. SCIACCA and M. CONDORELLI. 52 pages; 25 × 17.5 cm. 1960. S. Karger AG, Basel. Price, Sw Fr. 7.-

This monograph presents a morphologic and experimental study, combined with a critical review of the literature, of the involution of the ductus arteriosus. Multiple hypotheses and theories have been proposed to explain the closure of the patent ductus. The early theories tried to explain this process as purely passive in nature. Experimental work carried out in fetuses (1940–1950) led to the conclusions that an active process underlies the closure of the ductus, that closure takes place after birth, and that it is followed by involution of the ductus. The authors of this monograph question the reliability of the data obtained by previous workers, and attempt to re-evaluate them.

The object of the experimental work of Sciacca and Condorelli was to establish the effect of sudden interruption of blood flow in the ductus during gestation. In multiple studies conducted in several dozen guinea pigs in various stages of development, ligation of the ductus near term produced no change in the size of the heart,

nor did it endanger the fetus nor jeopardize its respirations. The electrocardiogram showed no evidence of right ventricular strain. Angiocardiograms showed that the pulmonary circulation was fully established. The ductus itself was always very difficult to visualize. Ligation of the ductus at midterm produced dilatation of the right side of the heart due to increase in pulmonary vascular resistance. Electrocardiographic evidence of right ventricular strain was produced immediately, but was of short duration. Ligation of the pulmonary artery and the patent ductus produced immediate distention of the heart, which in several fetuses was followed by ventricular fibrillation and death. Electrocardiographic changes compatible with marked sudden right ventricular strain were noted. Histologic studies showed that involution of the ductus in guinea pig fetuses results in arrest of growth, proliferation of intima with infiltration by mucoid material, and subsequent fibrosis of the media.

The authors conclude from their work that during the last period of fetal life the blood flows through the lungs and the ductus. This may be interpreted as an adaptation to the requirements of the newborn. The changes consist of gradual involution of the ductus with reduction in the blood flow through it, and progressive development of the circulation of the lungs.

The theories that attempt to explain involution of the ductus as taking place exclusively at birth receive no support from the work presented by Sciacca and Condorelli. It is their opinion that involution of the ductus is an intrinsic phenomenon entirely independent of any changes which affect it at birth.

This book is recommended to the experimental pathologist and embryologist interested in the involution of the ductus arteriosus. The interested cardiologist will find that this monograph supplies an excellent bibliography on the subject.

LUIS F. GONZALEZ, M.D.

Massage, Manipulation and Traction. Physical Medicine Library. Vol. 5. Edited by SIDNEY LICHT, M.D. 275 pages; 23.5 × 16 cm. 1960. Elizabeth Licht, New Haven, Conn. Price, $10.00.

This, the fifth volume of the Physical Medicine Library, is divided into three parts, as indicated by the title. Half of the book is devoted to massage, including physiologic effect, technics, and clinical applications. The discussions include those on connective tissue massage (bindegewebsmassage), syncardial massage, and mechanical methods, as well as the conventional types of massage. Part II is devoted to manipulation of the spine and the joints of the extremities, as well as stretching of contractures. Part III discusses the various methods of traction used for conditions other than fractures and dislocations.

Most of the book is very detailed and well illustrated. While the subject matter is quite controversial, every chapter contains some useful information concerning technics which are not, but should be, used by physicians in this country. This volume should interest physiatrists, orthopedists, neurologists, and neurosurgeons.

PAUL F. RICHARDSON, M.D.

Glaucoma: Transactions of the Fourth Conference, March 8, 9, and 10, 1959, Princeton, N. J. Edited by FRANK W. NEWELL, M.D. 257 pages; 23.5 × 16 cm. 1960. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $8.00.

Transactions of the Fourth Conference, dealing with glaucoma, is in direct contrast to the Third Symposium of 1958. The Third Conference was concerned mainly with clinical evaluation of the newer diagnostic aids. Since then the value of tono-

graphy in the diagnosis of sub-clinical and of suspected glaucoma is accepted as indisputable. The use of the tonograph not only in the diagnosis of glaucoma, but also in relationship to its clinical management, is covered very thoroughly; there are new concepts relating to the osmotic factors in the formation of aqueous. One provocative chapter deals with the consensual changes in intraocular pressure experimentally. The entire volume represents a concise and well-presented contribution to the study of glaucoma.

A very interesting appendix has been added to the book. In this section, the various participants mention their scholastic backgrounds, interests, and contributions to research. The study of glaucoma has attracted not only clinicians and physiologists, but chemists, physicists, neurologists, and anatomists.

The Fourth Conference deals mainly with anatomical factors, and the chapter dealing with the relationship of simple glaucoma to the anatomical structures in the angle of the anterior chamber is of limited value, but, as will be mentioned later on, the limitations are of potential and widespread expansion.

A new instrument has been used in the study of the angle of the anterior chamber, the trabecular meshwork, and the surrounding structures of the anterior segment of the eye. This is the electron microscope, and while many questions have been satisfactorily answered after one has studied photo-micrographs with this instrument, the impression is left with the reader that while a major stride has been made in the study of this part of the eye, nevertheless many obstacles were encountered that should stimulate much in the way of future studies.

There seems to be general approval by the participants in this conference that the concept of filtration at the angle of the anterior chamber should be discarded. Although no adequate term has been thus far substituted for the idea of filtration, microscopic sections studied from three different planes tend to corroborate the participants' opinions. The photo-micrographs are excellent, and while most of the features can be explained, there are many factors present that lend themselves to speculation rather than to definitive analysis. The presence of collagen, for instance, in the central zone of the trabecular meshwork is great, and diminishes as the canal of Schlemm is approached. The significance of collagen in this area is not known at present. Since the resistance to out-flow barrier was decreased by hyaluronidase, it was felt that there was a hyaluronidase-sensitive mucopolysaccharide in the trabecula. This was difficult to demonstrate in dead and enucleated eyes with present staining methods. Undoubtedly, there is a need for developing stains that may have a specific affinity for this particular area. In view of the influence of mucopolysaccharide in the angle of the anterior chamber, the question of glaucoma was taken up in detail, but there could be no demonstration of mucopolysaccharide in the trabecula.

Some of the participants questioned the use and principles of the electron microscope. The basic fundamentals of the electron microscope and interpretation of the structures seen in the photo-micrographs are briefly, but concisely and lucidly, presented. This digression proves to be of great help to the reader in so far as the rest of the book is concerned.

Other obstacles preventing any definite conclusions even with the use of the electron microscope were such factors as the following: Many of the eyes enucleated were treated thus for intraocular tumors. It is well known that intraocular tumors change the chemical composition of the anterior segment of the eye, so that the presence of these chemicals masks some of the findings. Transplanted meshwork was used, and it was noted that the vessels stopped at the trabecula but did proceed to the cornea, etc. Trabecula apparently repels vascularization. Post-mortem changes in the trabecular meshwork and Schlemm's canal are also misleading. The type of surgery used in the eyes that were treated for glaucoma and eventually enucleated also pro-

duced definite changes that could not be evaluated on the basis of simple glaucomatous changes.

In spite of the obstacles mentioned above, this presentation has opened many avenues of research that should be extremely stimulating. In general, it must be said that this is an extremely important, basic book. Not only is it of value to clinicians; the analysis of the ultra-structural patterns of the various structures should provide more intelligent understanding of the physiological activities that also occur.

Whether or not future medical or surgical treatment of glaucoma will change is open to question. If it does not, at least many of the problems surrounding the rationale of the treatment of glaucoma will be placed on a more reasonable basis. This book is a vital and integral part of the conferences on glaucoma.

JOHN C. OZAZEWSKI, M.D.

Gastric Cytology: Principles, Methods and Results. By RUDOLF OTTO KARL SCHADE, M.D. (Dunelm), M.D. (Tübingen), L.R.C.P., M.R.C.S. 83 pages; 25.5 × 19 cm. 1960. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. Price, $8.00.

This excellent little monograph details the author's experience in the cytologic diagnosis of gastritis and gastric cancer. Since 1954 he has done some 3,500 cytologic examinations with a diagnostic accuracy of 96.4% for carcinoma of the stomach.

In the first part of the book the author discusses cytology in general, methods of procedure, and assessment of smears. For the collection of gastric specimens preference is given to simple saline lavage. The second part of the book is concerned with the differential diagnosis of exfoliated cells and considers contaminating cells, carcinoma, pernicious anemia, and gastritis. Sources of diagnostic error are discussed. No opportunities were available to study noncarcinomatous tumors of the stomach. Thirty-seven pages of excellent black and white microphotographs appear at the end of the book to illustrate an easily read and lucid text.

The keynote to success in cytodiagnosis is experience, and one is impressed by the author's efforts to correlate his cytologic diagnosis with the histopathologic findings, experience gained by no other method. As a result of his studies the author joins Konjetzny to conclude that gastric carcinoma arises secondarily to chronic gastritis and to recommend gastric cytology for follow-up studies in cases of pernicious anemia and chronic gastritis in order to detect early malignancy.

This fine monograph will be welcomed by all who pursue the diagnosis of gastric disease.

J. EDWARD KELLY, JR., M.D.

Modern Nutrition in Health and Disease: Dietotherapy. 2nd Ed. Edited by MICHAEL G. WOHL, M.D., and ROBERT S. GOODHART, M.D. (59 contributors.) 1,152 pages; 24 × 15.5 cm. 1960. Lea & Febiger, Philadelphia. Price, $18.50.

This large volume represents the contributions of 59 recognized experts who intend to supply basic information on nutrition and its application to the practice of medicine. The book is divided into three parts, concerned with normal nutrition, nutrition in disease, and nutrition in periods of physiologic stress. The topics covered in 32 chapters concern all the sub-specialities of medical practice and each chapter is appended by a pertinent and current bibliography. While retaining clinical perspective a wealth of fundamental information is presented, primarily from a physiologic point of view, with a minimum of detailed biochemistry. This is the

second edition of this work in five years and with the rapid advances in the science of nutrition, it is likely that another five years will not be too soon for the next revision.

Since nutrition is of paramount importance in the therapy of gastrointestinal tract disease and since gut integrity is prerequisite for nutrition in any disease, it is disappointing that only 38 pages of the more than 1,000 pages of text are alloted to nutrition in diseases of the stomach and the intestinal tract. Even these few pages are not meaty with information based on fact. In addition, reading of the book is made difficult by the frequent lack of agreement between subject and verb, numerous mistakes in spelling, gross errors in grammar, and absence of commas between lengthy clauses. Some sentences are so disjointed that concepts will be missed completely.

The book is commendable in that it presents a unique compendium of data on nutrition. The book offers nothing to the established specialist or researcher in a particular field, but it will be of value as a text for medical students and as a reference volume for physicians.

J. Edward Kelly, Jr., M.D.

Toward the Diagnosis of Congenital Heart Disease. By W. Carleton Whiteside, M.D. 92 pages; 15.5 × 23.5 cm. 1960. Charles C Thomas, Springfield, Illinois. Price, $4.50.

The author of this brief volume is a cardiac surgeon conversant with the diagnostic problems in the field of congenital heart disease. His aim was to summarize for easy reference the signs and symptoms associated with congenital cardiovascular lesions and the differential diagnosis. For this purpose he has assembled statements, outlines and classifications gathered from cardiologists and cardiac surgeons throughout the world either through personal communication or from the literature. Relatively few of the individuals quoted are mentioned by name and the original reference is given in only two instances. There is no index.

The book starts with a brief section on general principles which contains random quotations many of which are of interest and value. The major part of the book consists of a discussion of 30 cardiovascular anomalies each of which is presented in an unsystematic outline form of varying degrees of completeness. In a rapidly growing field such as congenital heart disease any text will contain statements that are outdated by the time of publication or are not in accordance with the experience of a reviewer. Errors of this sort, such as occur in this book, may be forgiven and do not warrant mention. The material on the whole, however, is poorly arranged and the wording often ambiguous or so condensed as to be difficult of interpretation. There are many errors in proofreading.

This book would be confusing to the general practitioner or the beginning student in cardiology and of little value to experienced workers in the field of congenital heart disease.

R. A.

Metabolic Disturbances in Clinical Medicine. Edited by G. A. Smart, B.Sc., M.D., F.R.C.P. 358 pages; 24.5 × 16 cm. 1958. Little, Brown and Company, Boston. Price, $10.00.

This book contains thirteen chapters, each of which is actually a relatively short monograph, on the following subjects:

Subject	Author
Problems of General Nutrition in Clinical Medicine	G. A. Smart
Disturbances of Water and Electrolytes	D. A. K. Black
Metabolic Aspects of Renal Disease	D. A. K. Black
The Metabolic Disturbances Following Injury	G. M. Wilson F. D. Moore R. P. Jepson
Metabolic Aspects of Liver Disease	A. L. Latner
Cardiovascular Aspects of Metabolic Disease	D. S. Frederickson R. S. Gordon J. Orloff
Oedema in Chronic Congestive Heart Failure	J. Orloff
Atherosclerosis	D. S. Fredrickson
Lung Function and Acid-Base Balance	S. G. Owen
Oxygen Therapy	E. A. Pask
Metabolic Bone Disease	F. C. Bartter
Metabolic Disturbances and the Haematopoietic System	R. B. Thompson
Disturbances of Metabolism Affecting the Central Nervous System	J. D. Spillane

Of the authors, nine are from English universities, four from the National Institutes of Health, and one from the Harvard Medical School.

The eight chapters which this reviewer was reasonably capable of judging were disappointing—largely because they contained little that was not easily available elsewhere. This, plus a brevity that is unexpected in a monograph, left the impression that the individual authors had been limited in their presentations by either editorial or publishing policy.

On the other hand, each chapter, with the definite exception of No. 9, presents a fairly good overall picture of the subject and a good list of selected references. Since any one of the chapters can be read in about one-half hour, this book may have real value for persons desiring an introduction to one or more of the subjects covered.

As stated in Dr. Smart's preface, "The metabolism of disease is one of the most rapid growing-points of internal medicine. . . ." This is a truism recognized by at least two editors of current textbooks of medicine. It is believed that the two texts alluded to present most of the subjects covered in these monographs in better relation to internal medicine than has been achieved in this book.

B. W. A.

Diverticulitis. By SARA M. JORDAN, M.D., and RUSSELL S. BOLES, JR., M.D. 89 pages; 14 × 22.5 cm. 1960. Grune & Stratton, New York and London. Price, $4.75.

This monograph, begun by Dr. Jordan before her untimely death and completed by her Lahey Clinic associate, Dr. Russell S. Boles, Jr., is an outstanding review of colonic diverticulosis and diverticulitis. A thorough survey of the often contradictory literature, supplemented by the authors' carefully studied experience and considered opinions, is presented in a concise and lucid style. Pathogenesis, incidence, natural history, diagnosis, complications, medical therapy, and indications for surgery are discussed. The plan of management described for acute attacks is less intensive than that employed in some clinics, but this is a small point. The binding of the book, its print, illustrations, and organization of material are very satisfactory. The extensive reference list should be helpful to others working in this field.

The authors have gone as far as is presently possible to clarify our clinical knowledge of this subject. All physicians who treat gastrointestinal disease will benefit from their valuable contribution.

H. PHELPS POTTER, JR., M.D.

BOOK NOTICES

Human Pituitary Hormones, Ciba Foundation Colloquia on Endocrinology. Volume XIII. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.R.C.P., and CECILIA M. O'CONNOR, B.Sc. 336 pages. 1960. Little, Brown and Company, Boston.

This volume, the eighth in the distinguished series of *Ciba Foundation Colloquia on Endocrinology,* records the proceedings of an international symposium on human pituitary hormones held in Buenos Aires in August, 1959, under the chairmanship of Professor F. G. Young. The program included short essays on current research into the chemistry, biochemistry, and physiology of human growth hormone, follicle stimulating hormone, interstitial-cell stimulating hormone, adrenocorticotrophic hormone, melanophore-stimulating hormone, and thyroid stimulating hormone by such recognized authorities as Wilhelmi, Li, Raben, Beck, Gemzell, Lorraine, and Harris. Also included are a chapter on the radiologic anatomy of the human pituitary by Joplin and Fraser, and an account of the immunologic studies of human growth hormone carried out by Dr. C. H. Read in the course of developing a method for assaying this hormone in human serum. The publication of the open discussion which followed each presentation provides some of the most valuable and provocative material in the volume. The careful editing and indexing greatly facilitate the use of this book as a reference source for all those interested in current research in endocrinology.

ALBERT WINEGRAD, M.D.

Regulation of the Inorganic Ion Content of Cells. Ciba Foundation Study Group, No. 5. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and CECILIA M. O'CONNOR, B.Sc. 100 pages; 12.8 × 19 cm. 1960. Little, Brown and Company, Boston.

Seven investigators presented their recent studies of the active transport and cellular control of inorganic ions in a conference held at The Ciba Foundation, London, on April 6, 1960. Other guests took part in the discussion which followed the papers.

This little volume is a transcript of these papers and the discussions. The editors have added a list of citations, and an index.

EDWARD J. HUTH, M.D.

Artefacts and Handling and Processing Faults on X-ray Films. By Professor Dr. E. A. ZIMMER. 67 pages; 17.2 × 24.2 cm. 1960. Grune & Stratton, New York. Price, $5.75.

One hundred twenty-eight pictures show practically all the types of technical flaws that can be seen on processed roentgenographs. The text consists entirely of brief descriptions of the flaws illustrated and of their causes. Appropriate preventive remedies are suggested by the author for some of the defects.

Misinterpretations of roentgen findings are not likely to stem from the defects here illustrated; the greatest value of this little handbook will lie in its being used to correct errors made by sloppy or inexperienced technicians.

E. J. H.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. So far as is practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Actualités Pédiatriques: Deuxième Série. By Prof. MARCEL LELONG and others. Clinique de Pédiatrie et Puériculture de l'Hopital. 278 pages; 16.5 × 25 cm. 1960. G. Doin & Cie, Paris, France. Price, NF 32.

Bleeding Syndromes: A Clinical Manual. By OSCAR D. RATNOFF, M.D. 287 pages; 16 × 23.5 cm. 1960. Charles C Thomas, Springfield, Ill. Price, $8.50.

The Central Nervous System and Behavior. Transactions of the Third Conference, Princeton, N. J., Feb. 21–24, 1960. 460 pages; 16 × 23.5 cm. Josiah Macy Jr., Foundation, New York, N. Y., with the cooperation of The National Science Foundation, Washington, D. C. Price, $7.50.

Clinicopathological Conferences of the Massachusetts General Hospital. By BENJAMIN CASTLEMAN, M.D., and H. ROBERT DUDLEY, JR., M.D. 289 pages; 21.8 × 27.5 cm. 1960. Little, Brown and Company, Boston. Price, $12.50.

Cutaneous Manifestations of the Reticuloendothelial Granulomas. Publication No. 363, American Lecture Series, the Bannerstone Division of American Lectures in Dermatology. Edited by SAMUEL M. BLUEFARB, M.D., F.A.C.P. 410 pages; 14.5 × 22 cm. 1960. Charles C Thomas, Springfield, Ill. Price, $14.50.

Farmacologia: Materia Medico y Terapeutica. Vol. III. By LUIS CAMPONOVO and ALFREDO BANDONI. 1,923 pages; 16.5 × 23 cm. 1960. Lopez & Etchegoyen, Buenos Aires, Argentina.

Handbook of Physiology. Section 1: Neurophysiology. Vol. III. By JOHN FIELD, Editor-in-Chief, H. W. MAGOUN, Section Editor, and VICTOR E. HALL, Executive Editor. 1,965 pages; 22.5 × 28.8 cm. 1960. Distributed for the American Physiological Society by The Williams & Wilkins Co., Baltimore, Md. Price, $20.00.

Heart Sounds and Murmurs: A Clinical and Phonocardiographic Study. By P. A. ONGLEY, M.D., M. B. RAPPAPORT, M.D., HOWARD B. SPRAGUE, M.D., and A. S. NADAS, M.D. 360 pages; 18 × 26 cm. Grune & Stratton, New York. Price, $9.75.

La Physiologie des Sinus ses Applications Cliniques et Therapeutiques. By L. FLOTTES, P. CLERC, R. RIU, and F. DEVILLA, with the collaboration of R. GUILLERM, R. BADRE, and R. LEDEN. 592 pages; 15.5 × 24 cm. 1960. Librairie Arnette, Paris. Price, NF 75.

La Traitement de la Paralysie Faciale après Fracture du Rocher. Techniques chirurgicales Mécanisme de la Récupération. By G. F. GREINER, G. KLOTZ, and J. GAILARD, with the collaboration of F. ISCH. 182 pages; 15.6 × 23.8 cm. 1960. Librairie Arnette, Paris. Price, NF 25.

Les Cirrhoses due Foie: Bases Étio-Pathogéniques et Physio-Pathologiques de Leur Traitement. By F. DARNIS and J. DUBRISAY. 342 pages; 16 × 24.5 cm. 1960. G. Doin & Cie, Paris. Price, NF 48.

Manual of Care for the Disabled Patient. By ARTHUR J. HEATHER, M.D. 104 pages; 14.5 × 21.5 cm. 1960. The Macmillan Company, New York. Price, $3.75.

Quantitative Cellular Haematology. By J. M. YOFFEY, D.Sc., M.D., F.R.C.S. 122 pages; 15.5 × 23.5 cm. 1960. Charles C Thomas, Springfield, Ill. Price, $5.50.

Quantitative Vectorelectrocardiography. By LOUIS BRINBERG, M.D. 123 pages; 17.8 × 26 cm. 1960. Waverly Press, Inc., Baltimore, Md.

Radioisotope Laboratory Techniques. 2nd Ed. By R. A. FAIRES and B. H. PARKS. 236 pages; 14.5 × 22 cm. 1960. Pitman Publishing Corp., New York. Price, $5.75.

Respiration. Physiologic Principles and Their Clinical Applications. By PETER C. LUCHSINGER, M.D., and KENNETH M. MOSER, M.D. 494 pages; 17.5 × 25.3 cm. 1960. The C. V. Mosby Co., St. Louis, Mo. Price, $15.75.

Surgical Disease of the Pancreas. By JOHN M. HOWARD, M.D., and GEORGE L. JORDAN, JR., M.D., and eight other contributors. 588 pages; 18.5 × 26 cm. 1960. J. B. Lippincott Co., Philadelphia. Price, $20.00.

Surgical Treatment of Trauma. Edited by PRESTON A. WADE, M.D., with 35 contributors. 760 pages; 18 × 24.5 cm. 1960. Grune & Stratton, New York. Price, $26.50.